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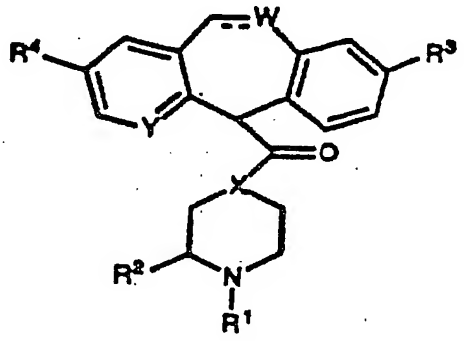
(54) Title: TRICYCLIC COMPOUNDS USEFUL FOR INHIBITION OF FARNESYL PROTEIN TRANSFERASE

(57) Abstract

Novel compounds of Formula (1.0) are disclosed. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering a compound of Formula (1.0) to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human being.



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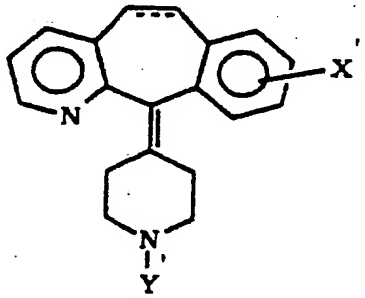
TRICYCLIC COMPOUNDS USEFUL FOR INHIBITION OF FARNESYL PROTEIN TRANSFERASE

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:



wherein Y' is hydrogen, substituted carboxylate or substituted sulfonyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

A welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

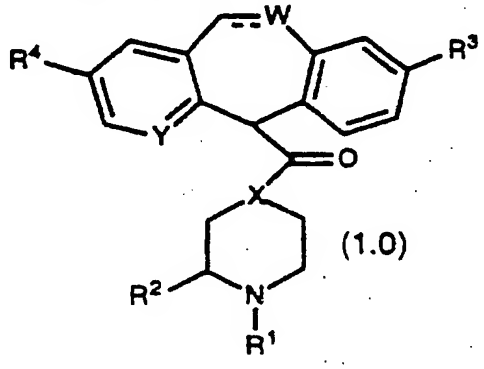
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein

transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

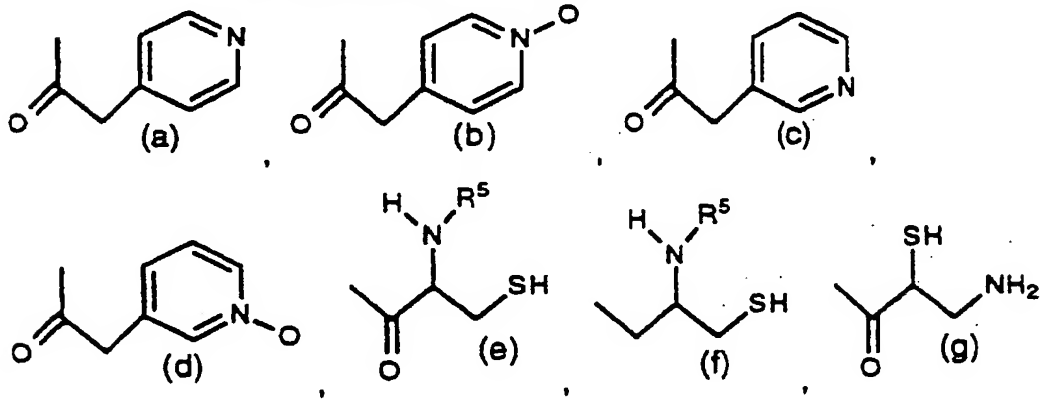
The compounds useful in the claimed methods are novel compounds represented by Formula 1.0:

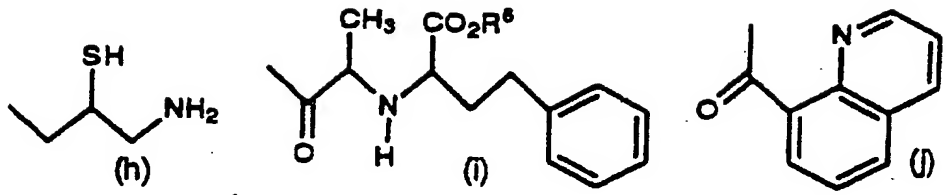


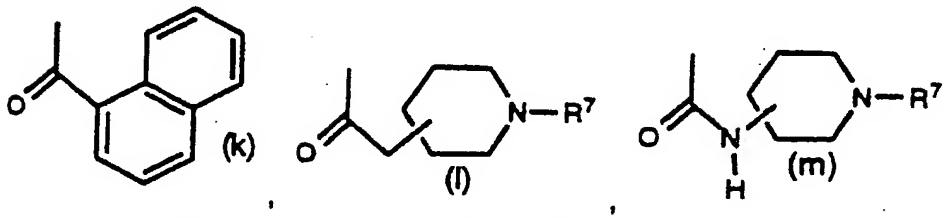
(1.0)

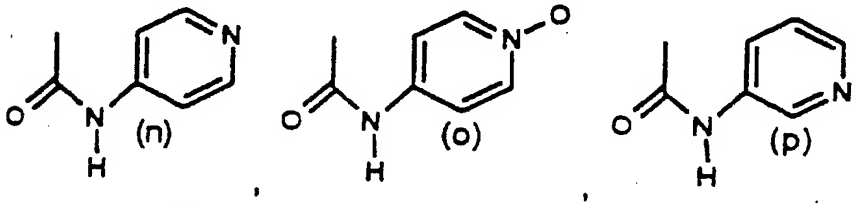
or a pharmaceutically acceptable salt or solvate thereof, wherein:

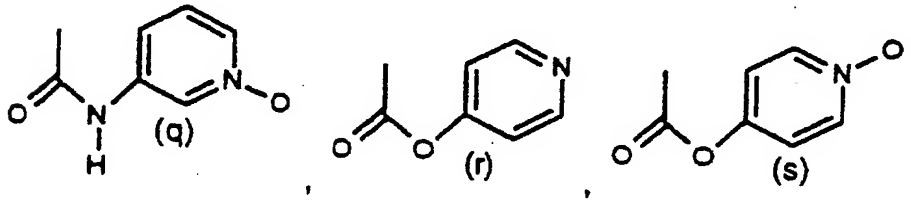
(1) R^1 is a group selected from:

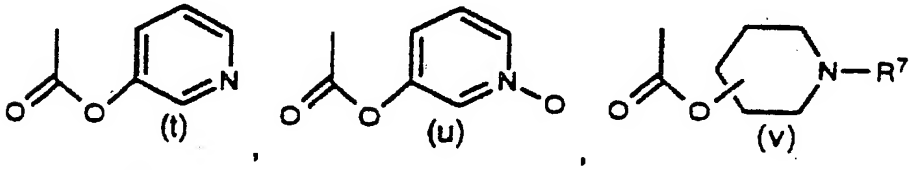


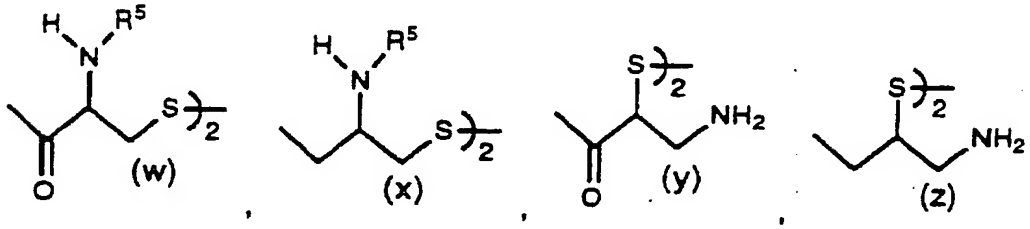


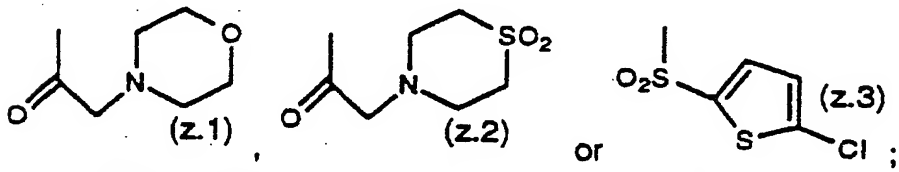












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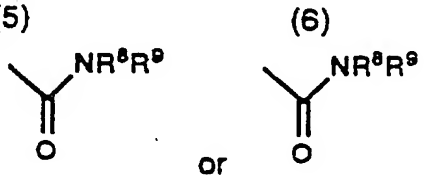
R^2 is selected from: (1) H, (2) C_1 to C_8 alkyl, (3) C_2 to C_8 alkenyl, (4) C_2 to C_8 alkynyl,



wherein said alkyl, alkenyl, or alkynyl is optionally substituted with one or more groups independently selected from:

(a) aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl; said aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl optionally substituted with one or more groups independently selected from:

(1) C_1 to C_4 alkyl,

(2) $(CH_2)_tOR^8$ wherein t is 1 to 4,

(3) $(CH_2)_tNR^8R^9$ wherein t is 1 to 4, or

(4) halogen,

(b) C_3 to C_6 cycloalkyl,

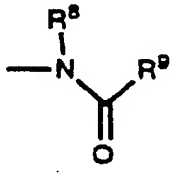
(c) $-OR^8$,

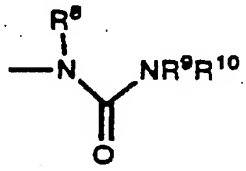
(d) $-SR^8$,

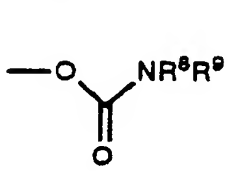
(e) $-S(O)R^8$,

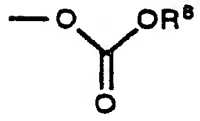
(f) $-SO_2R^8$,

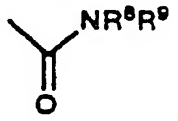
(g) $-NR^8R^9$,

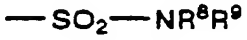
(h) 

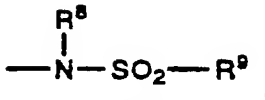
(i) 

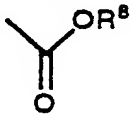
(j) 

(k) 

(l) 

(m) 

(n) 

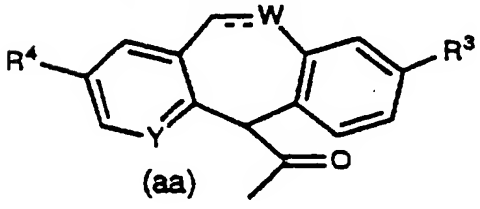
(o) 

;

R^3 is selected from H, halogen or C_1 to C_6 alkyl (e.g., methyl);

R^4 is selected from H, halogen or C_1 to C_6 alkyl (e.g., methyl);

R^5 is selected from: H,



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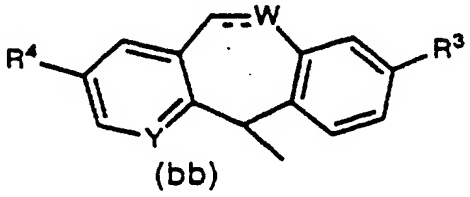

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R^6 is selected from H or C_1 to C_6 alkyl (preferably methyl or ethyl);

R^7 is selected from H, C_1 to C_6 alkyl, haloalkyl, or $-C(O)R^{11}$ wherein R^{11} is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy or $-NHR^{12}$ (wherein R^{12} is C_1 to C_6 alkyl or H), or R^7 is an acyl radical of a naturally occurring amino acid;

R^8, R^9 and R^{10} are independently selected from H, C_1 to C_4 alkyl, C_3 to C_6 cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl; said alkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl are optionally substituted with C_1 to C_4 alkoxy, aryl, heteroaryl, heterocycloalkyl, cyclopropyl, halogen, -OH, $-C(O)R^{13}$, $-SO_2R^{13}$, or $-NR^{14}R^{15}$ wherein R^{13} is selected from C_1 to C_4 alkyl or aralkyl, and wherein R^{14} and R^{15} are independently selected from H, C_1 to C_4 alkyl or aralkyl; with the proviso that R^8 is not H in substituents (e), (f) or (k), and with the proviso that R^9 is not H in substituent (h) or (n), and with the proviso that R^8, R^9, or R^{10} is not $-CH_2OH$ or $-CH_2NR^{14}R^{15}$ when R^8, R^9, or R^{10} is directly attached to a heteroatom (e.g., O, S or N).

optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which they are bound, form a 5 to 7 membered heterocycloalkyl ring;

optionally, when R^9 and R^{10} are bound to the same nitrogen, R^9 and R^{10}, together with the nitrogen to which they are bound, form a 5 to 7 membered heterocycloalkyl ring;

---- represents an optional bond;

W is selected from CH when the optional bond is present, or O, S or CH_2 when the optional bond is absent;

X is selected from CH or N; and

Y is selected from N or CH.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous

leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

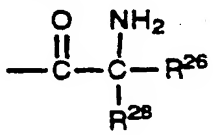
The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

Ac - represents acetyl;

acyl radical of a naturally occurring amino acid - means a group of the formula $-C(O)C(NH_2)R^{26}R^{28}$, i.e.:



wherein R^{26} and R^{28} represent the substituents of the amino acid bound to the α-carbon; for example R^{26} and R^{28} can be independently selected from H, alkyl, or alkyl substituted with an R^{30} group, wherein R^{30} can be, for example, -OH, SH, $-SCH_3$, $-NH_2$, phenyl, p-hydroxyphenyl, indolyl or imidazolyl, such that $HO-C(O)C(NH_2)R^{26}R^{28}$ is an amino acid selected from, for example, alanine, cysteine, cystine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, tryptophane, tyrosine or valine;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by aryl groups, as defined below (e.g., benzyl);

aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, $-COOR^{16}$ (wherein R^{16} represents H, alkyl, aryl or aralkyl (e.g., benzyl)), or $-NO_2$; and

Bu - represents butyl;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

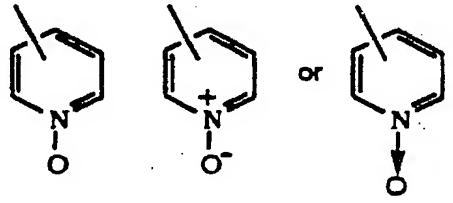
Et - represents ethyl;

halogen (halo)-represents fluoro, chloro, bromo and iodo;

haloalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by halogen atoms;

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or -N- (suitable heterocycloalkyl groups include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, etc.);

heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



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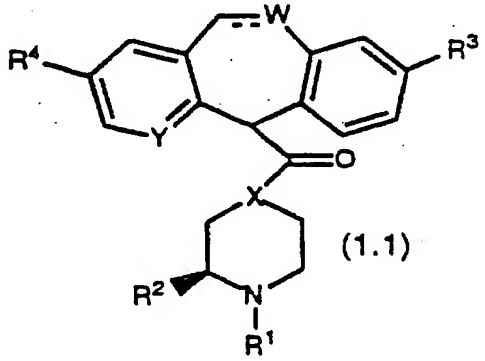
heteroarylalkyl - represents an alkyl group (as defined above) wherein one or more hydrogen atoms have been replaced by heteroaryl groups (as defined above); and

Ph - represents phenyl.

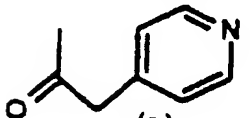
Representative compounds of the present invention include:

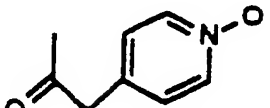


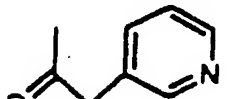
(1.1)

For the compounds of this invention, W is preferably CH or CH_2, with CH_2 being most preferred; Y is preferably N; X is preferably N; R^3 is preferably halogen, with Br, Cl or I being most preferred, and Cl being even more preferred; and R^4 is preferably halogen, with Br, Cl or I being most preferred, and Br being even more preferred.

Representative compounds of this invention include those wherein R^1 is selected from:


(a)


(b)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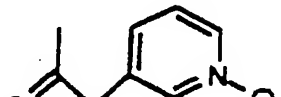
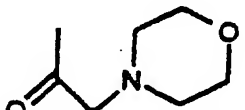
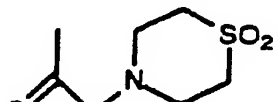

(d)

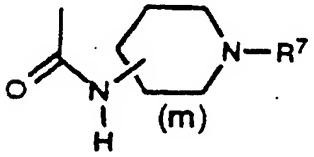

(l)

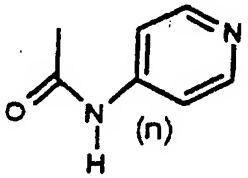

(z.1)

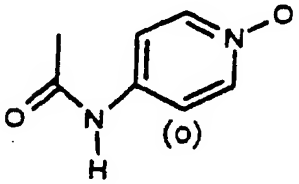
or

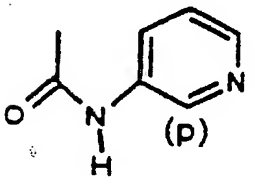

(z.2)

Representative compounds of this invention also include those wherein R^1 is selected from:

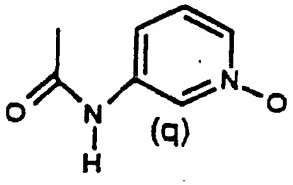

(m)


(n)

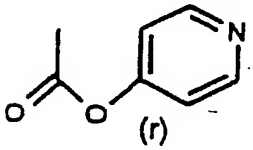

(o)

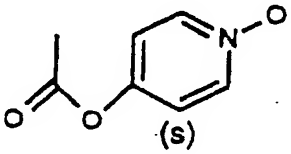

(p)

or


(q)

Representative compounds of this invention include compounds wherein R^1 is selected from:


(r)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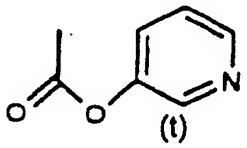
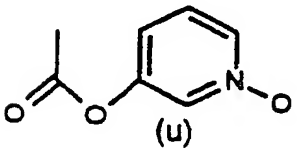
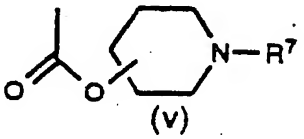
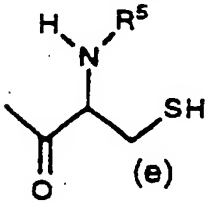

(t)

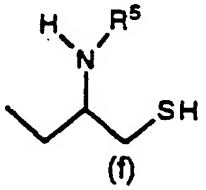

(u)

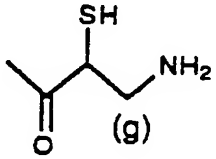
or


(v)

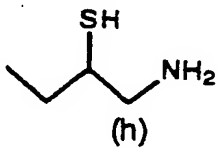
Representative compounds of this invention further include compounds wherein R^1 is selected from:


(e)

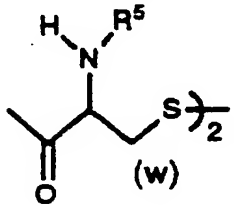

(f)

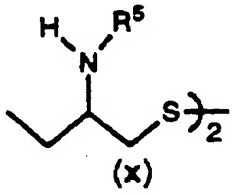

(g)

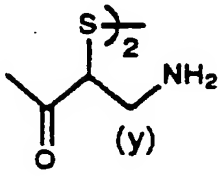
or


(h)

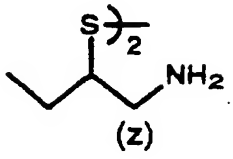
Representative compounds of this invention also include compounds wherein R^1 is selected from:


(w)

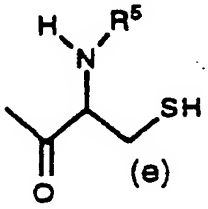

(x)


(y)

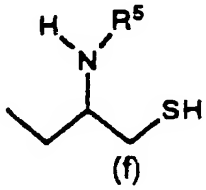
or


(z)

Generally R^1 is


(e)

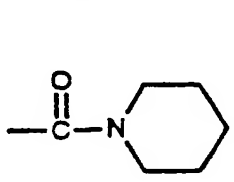
or

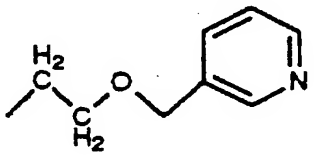

(f)

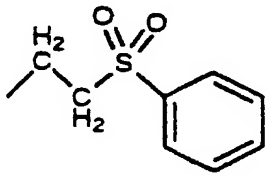
and usually R^1 is represented by Formula (e) or (f) above wherein R^5 is hydrogen.

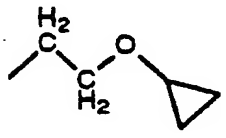
Those skilled in the art will appreciate that R^1 substituents (e), (f), (g) and (h) can exist as the disulfide substituents (w), (x), (y) and (z), respectively.

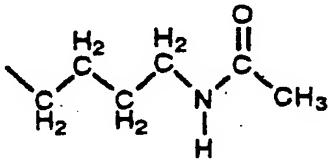
Preferably, R^2 is selected from H, $-C_4H_9$, $-CH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2O$-n-C_3H_7, $-CH_2CH_2CH_2OCH_3$,



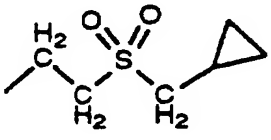








or



Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These

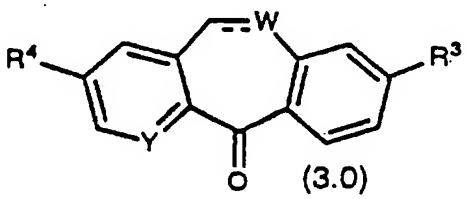
compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

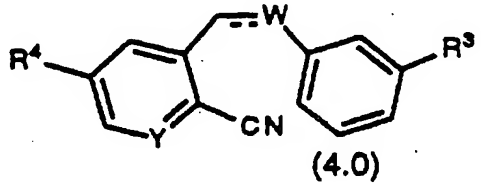
The following processes may be employed to produce compounds of the invention. Various intermediates in the processes described below can be produced by methods known in the art, see for example, U.S. 3,409,621, U.S. 5, 089,496, WO89/10369, WO92/20681, WO93/02081, and WO95/00497; the disclosures of each being incorporated herein by reference thereto.

Compounds of the invention can be produced from ketones of Formula 3.0:



(3.0)

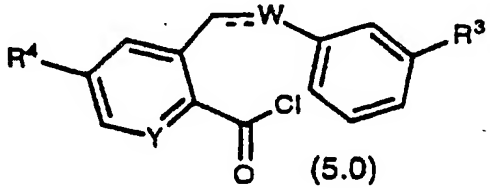
as described below. Compounds of Formula 3.0 are known or can be prepared by the procedures described in U.S. 5, 089,496, WO89/10369, WO92/20681, and WO93/02081. For example, intramolecular cyclization of a nitrile of Formula 4.0:



(4.0)

using a strong acid, such as CF_3SO_3H, at a temperature of about -15 to about 100°C, to form an imine intermediate which is hydrolyzed with water or aqueous acid to form the ketone of Formula 3.0

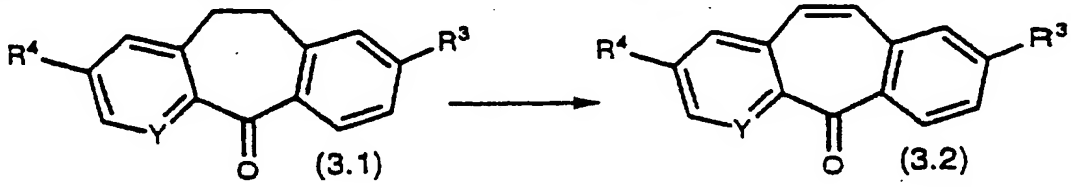
Alternatively, intramolecular Friedel-Crafts acylation of an acid chloride of Formula 5.0:



(5.0)

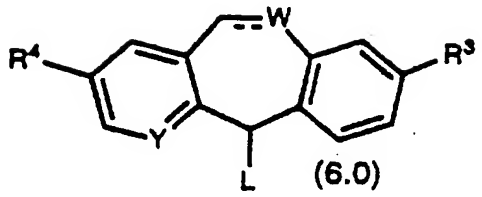
may also provide the desired ketone of Formula 3.0. The reaction may be carried out under the usual Friedel-Crafts conditions in an inert solvent and in the presence of a Lewis acid such as aluminium chloride. Acid chlorides of Formula 5.0 can be obtained by the hydrolysis of a compound of Formula 4.0 to the corresponding carboxylic acid. Typically this can be done by heating with an aqueous acid (e.g., aqueous HCl), followed by conversion of the acid to the acid chloride of Formula 5.0 under standard conditions well known to those skilled in the art (e.g., by treating with $SOCl_2$ or oxalyl chloride).

Ketones of Formula 3.2 (i.e., compounds of Formula 3.0 wherein W is CH) can be prepared by heating a compound of Formula 3.1 (i.e., a compound of Formula 3.0 wherein W is CH_2) with SeO_2 in acetic acid.



(3.1) (3.2)

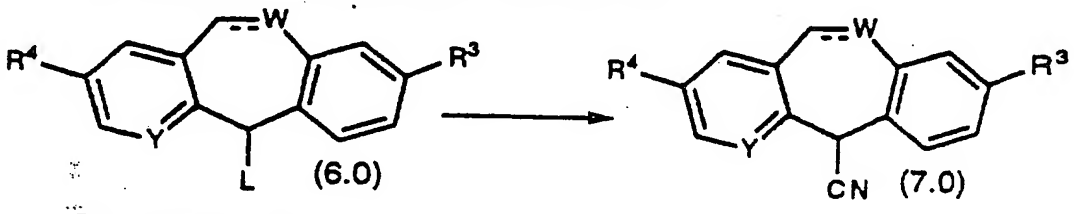
The ketone of Formula 3.0 is converted to the compound of Formula 6.0



(6.0)

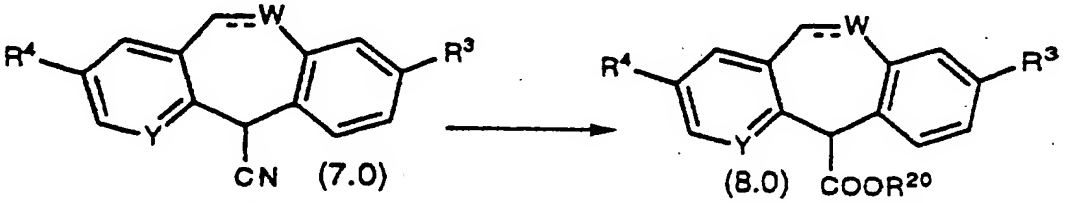
wherein L is Cl by a procedure analogous to that described in U.S. 3,409,621. For example, the ketone of Formula 3.0 is reduced to the corresponding alcohol using reagents such as sodium borohydride, and then the hydroxy group is converted to Cl by using a reagent such as thionyl chloride in benzene as a solvent. One skilled in the art can convert the hydroxy group to other leaving groups (e.g., Br, I, mesyloxy or tosyloxy).

The compound of Formula 6.0 (wherein L is Cl) is reacted, at a temperature of about 25° to about 100°C, with a cyanide salt (e.g., CuCN AgCN or NaCN) in a suitable organic solvent, such as pyridine or benzene, to produce the nitrile of Formula 7.0.



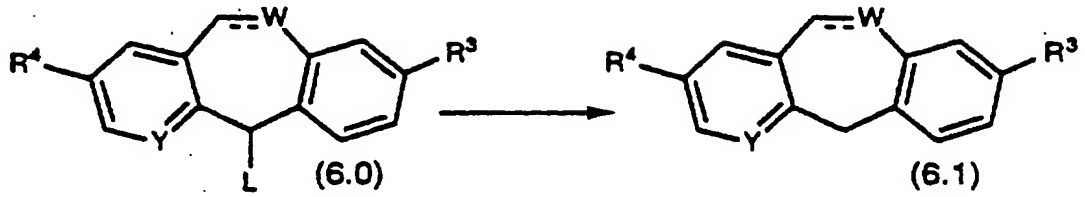
(6.0) (7.0)

The nitrile of Formula 7.0 can be hydrolyzed to an acid (Formula 8.0 wherein R^{20} is H), or an ester (Formula 8.0 wherein R^{20} is $-CH_3$). Hydrolysis can be accomplished using an aqueous acid (e.g., HCl), or an acid (e.g., p-toluenesulfonic acid or H_2SO_4) and an alcohol (e.g.,methanol or ethanol). The hydrolysis is carried out at a temperature of about 25° to about 80°C.



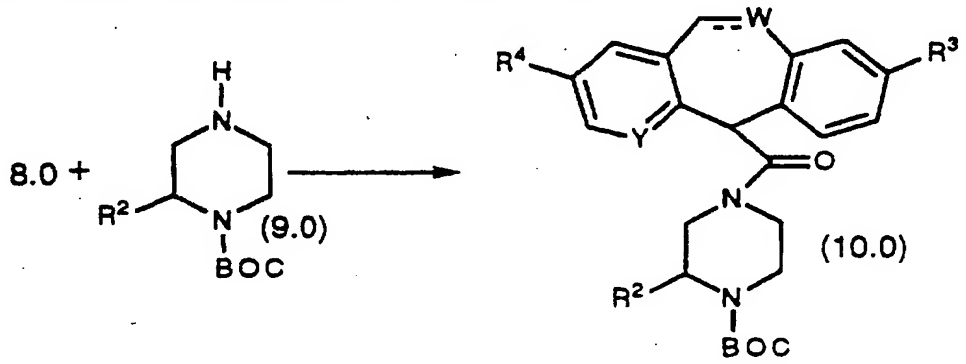
(7.0) (8.0) $COOR^{20}$

Alternatively, the compound of Formula 6.0 is reduced to the compound of formula 6.1 with a reducing agent, such as sodium borohydride, and a solvent, such as ethanol. The reduction is conducted at a temperature of about 25°C. The compound of Formula 6.0 can also be reduced to the compound of Formula 6.1 with zinc and acetic acid using a temperature of about 25° to about 100°C (usually about 80°C).



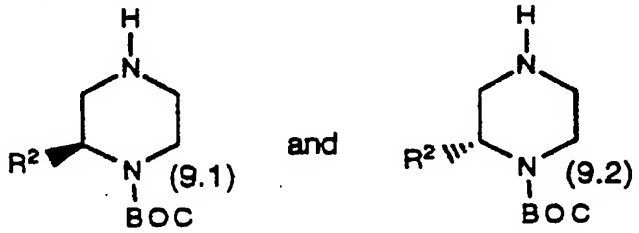
The compound of Formula 6.1 can be converted directly to a carboxylic acid of Formula 8.0 by treatment with a base such as n-butyl lithium followed by carbon dioxide.

The compound of Formula 8.0 is then reacted with a compound of Formula 9.0 to produce the compound of Formula 10.0. When the compound of Formula 8.0 is an acid (i.e., R^{20} is H), the reaction is conducted with a coupling reagent (such as a carbodiimide, e.g., dicyclohexylcarbodiimide) in a suitable solvent (such as DMF, i.e., N,N-dimethylformamide) at room temperature. When the compound of Formula 8.0 is an ester (i.e., R^{20} is $-CH_3$), the reaction is conducted in the presence of a base (e.g., triethylamine) in a suitable solvent (e.g., DMF) using elevated temperatures (e.g., about 100°C).



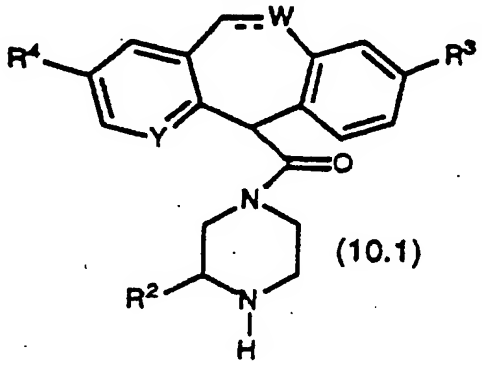
BOC is t-butyloxycarbonyl.

Those skilled in the art will appreciate that the compound of Formula 9.0 can exist as the two enantiomers



and preferably the enantiomer of Formula 9.1 is used to make the compounds of the invention. When the compound of Formula 9.1 is used compounds of formula 1.1 are obtained.

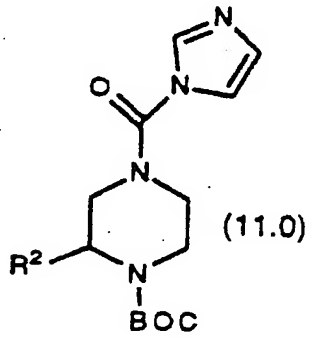
The compound of Formula 10.0 can be deprotected (i.e., the BOC group removed) by treatment with an acid (e.g.,trifluoroacetic acid, or HCl-dioxane) to produce the compound of Formula 10.1:



(10.1)

The compound of Formula 10.1 can be converted to the compound of Formula 1.1, wherein X is N, by acylation or reductive alkylation.

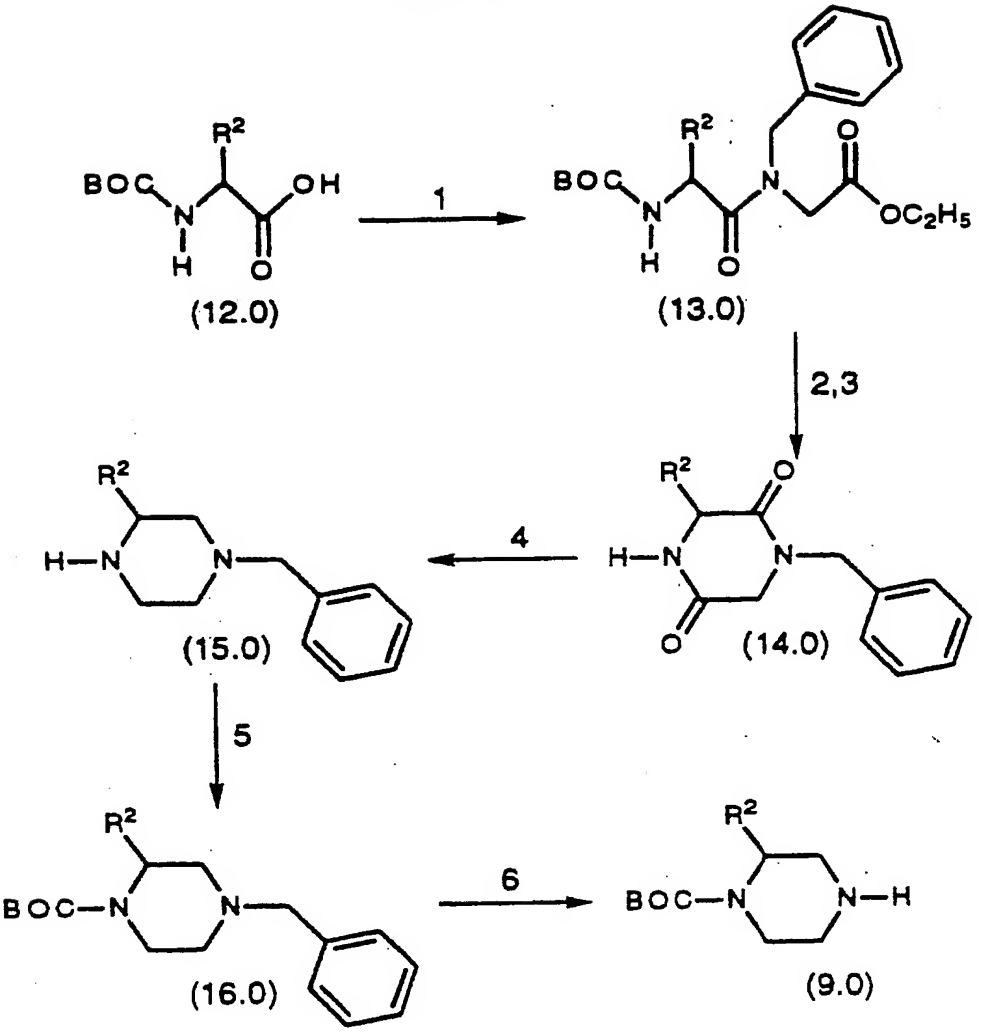
Alternatively, the compound of Formula 9.0 can be reacted with carbonyldiimiazole at about 0°C using methylene chloride to produce a compound of Formula 11.0:



(11.0)

The compound of Formula 6.1 can be treated with butyl lithium, and then reacted with the compound of Formula 11.0 to produce the compound of Formula 10.0. The compound of Formula 10.0 can then be deprotected as described above to produce the compound of Formula 10.1.

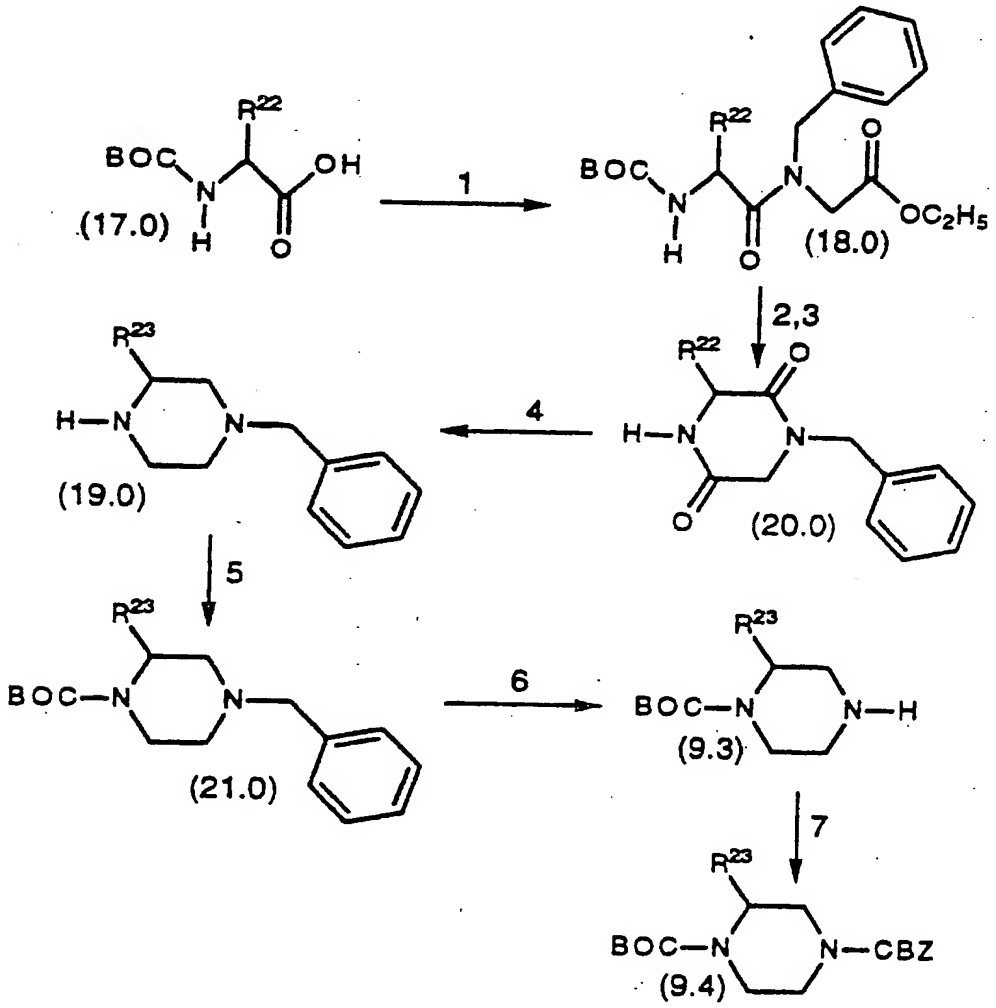
SCHEME 1



Scheme 1 describes the synthesis of 2-substituted piperazines wherein R^2 is H, alkyl, alkenyl, or alkynyl. Scheme 1 also describes the synthesis of 2-substituted piperazines wherein R^2 is alkyl, alkenyl, or alkynyl which are substituted with substituent groups (a), (b), (c), (d) and (g) as defined above, with the exception that R^8 and R^9 can not be a group that is substituted with $-C(O)R^{13}$ or $-SO_2R^{13}$. In Scheme 1, BOC-protected amino acids (12.0) are available commercially or can be made by procedures well known in the art. These amino acids can be coupled (step 1) to a commercially availble N-benzylglycine ethyl ester using suitable coupling agents such as DCC (dicyclohexylcarbodiimide) or DEC (1- ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in suitable solvents (e.g., N, N-dimethylformamide, chloroform or methylene chloride) to produce a compound of Formula 13.0. Generally, this reaction is conducted at room temperature (i.e., about 25°C). The BOC protecting

group is removed (step 2) at room temperature with suitable reagents such as trifluoroacetic acid, or hydrogen chloride in chloroform or dioxane. The deprotected dipeptide is cyclized (step 3) under basic conditions to produce the compound of Formula 14.0. The compound of Formula 14.0 is then reduced (step 4) using $LiAlH_4$ in refluxing ether (diethyl ether) or THF to give the piperazine of Formula 15.0. The unsubstituted nitrogen of the piperazine of Formula 15.0 is protected (step 5) with a BOC group by procedures well known in the art to give the compound of Formula 16.0. The N-benzyl group is removed (step 6) by catalytic hydrogenation (e.g., using Pd/C and hydrogen gas under pressure of about 60 psi) to give the compound of Formula 9.0.

SCHEME 2



Compounds of Formula 9.0, wherein R^2 represents alkyl, alkenyl or alkynyl substituted with (a), (c), (d) or (g) groups wherein R^8 or R^9 are substituted with $-C(O)R^{13}$ or $-S(O)_2R^{13}$ are made according to the process

of Scheme 2. Compounds of Formula 9.0, wherein R^2 represents $-C(O)NR^8R^9$ or $-C(O)OR^8$, or wherein R^2 represents alkyl, alkenyl or alkynyl substituted with a group (e), (f), or (h)-(o) are also made according to the process of Scheme 2. Compounds of Formula 17.0 (wherein R^{22} is an alkyl, alkenyl or alkynyl group containing either a -OH group, a -COOH or its corresponding ester) are available commercially or can be made by procedures known in the art. In Scheme 2, the compound of Formula 17.0 is reacted according to the procedures described for Scheme 1 (steps 1 to 4) to produce a compound of Formula 19.0 wherein R^{23} is a hydroxy substituted alkyl, alkenyl or alkynyl group. The compound of Formula 19.0 is then protected with a BOC group and then debenzylated according to the procedures in Scheme 1 (Steps 5 and 6) to produce a compound of Formula 9.3. The unsubstituted nitrogen of the compound of Formula 9.3 is protected (step 7) with a CBZ group (benzyloxycarbonyl) by procedures known in the art to produce the compound of Formula 9.4.

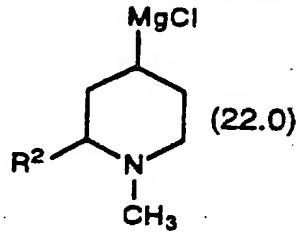
When R^{23} is $-CH_2OH$, the hydroxy group can be oxidized to produce the corresponding carboxyl group-(COOH). This carboxyl group can them be esterified to produce compounds wherein R^2 is $-C(O)OR^8$, or the carboxyl group can be converted to amides to produce compounds wherein R^2 is $-C(O)NR^8R^9$ by procedures well known in the art.

To produce compounds of formula 9.0 in Scheme 2 wherein R^2 is a substituent other than $-C(O)OR^8$ or $-C(O)NR^8R^9$ (i.e., substituents (5) and (6)), the hydroxy group on R^{23} can be converted to a leaving group, such as chloro, mesyloxy or tosyloxy, by techniques well known in the art. Then the leaving group can be displaced by various nucleophiles such as organometallics (to produce R^2 with an (a) substituent), thiols (to produce R^2 with a (d) substituent), sulfenyls (to produce R^2 with an (e) substituent), sulfinyls (to produce R^2 with an (f) or (m) substituent), amines (to produce R^2 with a (g) substituent), and alcohols (to produce R^2 with a (c) substituent). The hydroxy group on R^{23} can also be acylated (to produce R^2 with a (j) or (k) substituent) or alkylated (to produce R^2 with a (c) substituent). When R^{23} is alkyl having more than one carbon atom, or alkenyl or alkynyl, the hydroxy group can be oxidized, as discussed above, to produce the corresponding carboxyl group (i.e., substituent (o) wherein R^8 is H). This carboxyl group can be esterified to produce compounds wherein substituent (o) is $-C(O)OR^8$ wherein R^8 is other than H, or converted to amides to produce to produce R^2 with an (l) substituent by procedures well known in the art. When the leaving group is displaced

by an amine (e.g., -NR^8R^9), the amine can then be converted to R^2 substituent groups (h), (i) or (n) by reacting the amine with an acyl halide (to produce R^2 with an (h) substituent), a carbamyl halide (to produce R^2 with an (i) substituent) or a sulfonyl halide (to produce R^2 with an (n) substituent) by procedures well known in the art.

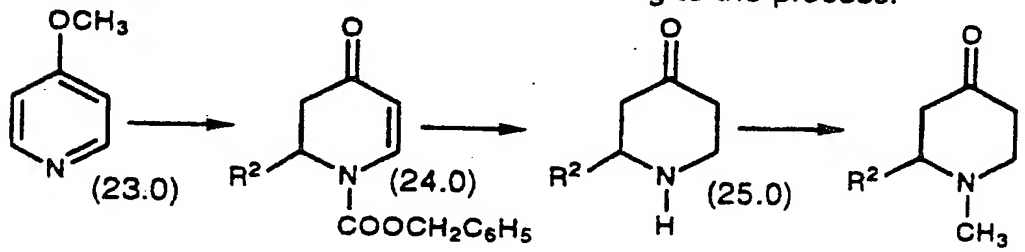
The preparation of compounds of Formula 9.0 is described in WO 95/00497, published January 5, 1995, the disclosure of which has already been incorporated herein by reference thereto.

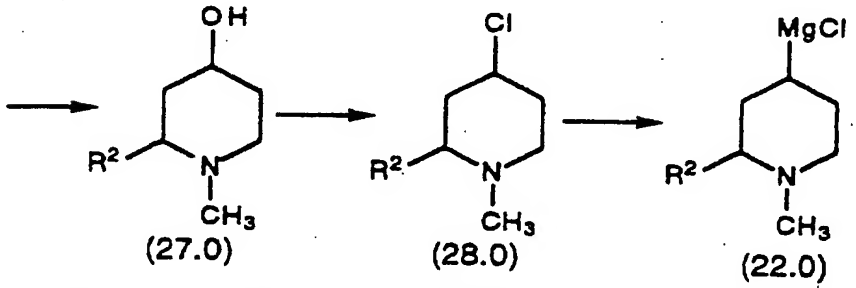
Compounds of Formula 1.0 wherein X is CH, and R^2 is alkyl, alkenyl or alkynyl, or R^2 is alkyl, alkenyl or alkynyl substituted with substituents (a), (b), (c), (d), or (g) with the exception that substituents R^8 or R^9 cannot have a halogen, -OH, -$C(O)R^{13}$ or -SO_2R^{13} substituent, can be made from compounds of the Formula 22.0:



(22.0)

Compound 22.0 can be made according to the process:

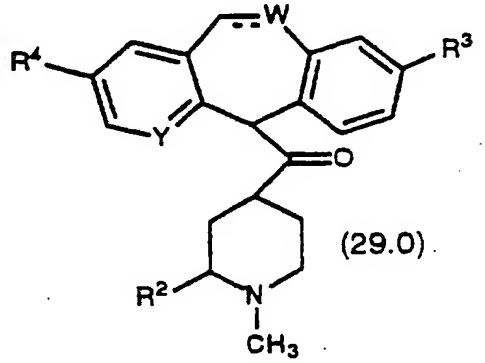




The substituted piperidines of Formula 22.0 may be prepared, as racemic mixtures, by essentially the same methods as described in D.L. Comins and J.D. Brown, Tetrahedron Letters, vol. 27 No. 38, pgs. 4549 -4552, 1986. Thus, 4-methoxypyridine (23.0) may be converted using a variety of alkyl Grignard reagents (wherein R^2 is as illustrated below) and

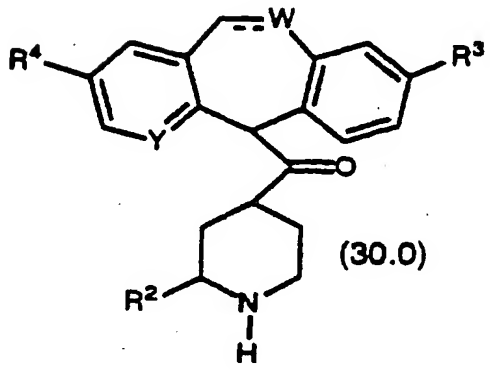
benzylchloroformate to the desired unsaturated ketopiperidines (24.0). Removal of the benzylcarbamoyl group with concomitant reduction of the double bond by catalytic hydrogenation yields the substituted ketopiperidines (25.0). Alternatively, the benzylcarbamoyl group can be removed with either base or acid followed by metal hydride reduction of the double bond to produce the compound of Formula 25.0. Alkylation of the compound of Formula 25.0 with a suitable alkyl iodide such as methyl iodide in the presence of sodium hydride gives the n-alkylketopiperidines (26.0). Reduction of the compound of Formula 26.0 with sodium borohydride affords the hydroxypiperidine of Formula 27.0. The compound of Formula 27.0 is reacted with a suitable chlorinating agent such as thionyl chloride to afford the 4-chloropiperidine of Formula 28.0 which may in turn be converted by reaction with magnesium into the compound of Formula 22.0.

The compound of Formula 22.0 is reacted with the compound of Formula 7.0, described above, in a suitable solvent such as diethyl ether or THF. The reaction is conducted at room temperature (about 25°C) to about 50°C. This reaction is then followed by aqueous acid hydrolysis to yield ketones of the Formula:



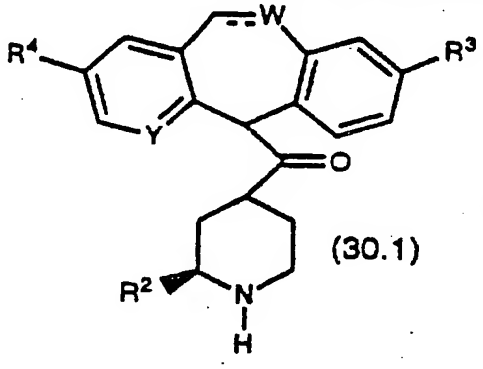
(29.0)

The N-methyl group on the piperidine ring can be converted to a carboethoxy group (-$COOC_2H_5$) by reaction with excess ethyl chloroformate in dry toluene containing triethylamine at a temperature of about 80°C. This procedure is similar to that described in U.S. Patents 4,282,233 and 4,335,036. The carboethoxy group can be removed by either acid or base hydrolysis to give the compound of Formula 30.0:



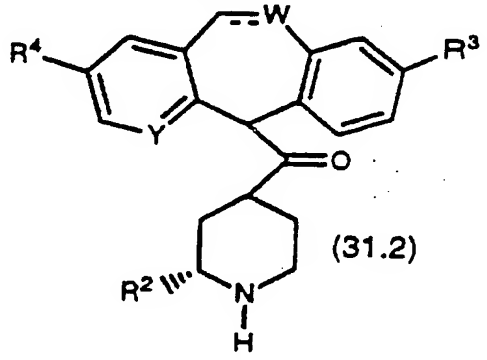
(30.0)

The compounds of Formula 30.0 are prepared as diasteromeric mixtures. Preferably, the diasteriomers are separated into single isomers by classical resolution methods or by chiral HPLC to yield:



(30.1)

and



(31.2)

The compound of Formula 30.0, preferably 30.1, can be converted to the compound of Formula 1.0 (preferably 1.1), wherein X is CH, by acylation or reductive alkylation. .

Acylation of the compounds of Formulas 10.1 and 30.0 can be carried out by reacting the compound of Formula 10.0 or 30.0 with the corresponding carboxylic acid of the desired R^1 group with a coupling agent, such as a carbodiimide such as dicyclohexylcarbodiimide(DCC) or DEC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). The acylation reaction can be carried out in a suitable organic solvent such as DMF, THF or methylene chloride at a temperature of about -10° to about 100°C, preferably at about 0° to about 50°C, and most preferably about room temperature. When the coupling reagent is DCC or DEC, the reaction is preferably conducted in the presence of HOBT.

Compounds of Formula 1.0, wherein R^1 is a substituent (a), (b), (c), (d), (e), (g), (i), (j), (k), (l), (z.1), (z.2) or (z.3) can be made by reacting a compound of Formula 10.1 or 30.0 with R^1-L, wherein L is a leaving group such as Cl, Br, I, or a carboxylate (an anhydride). The reaction is carried

out in the presence of a base, preferably a tertiary amine such as triethylamine or N-methyl morpholine.

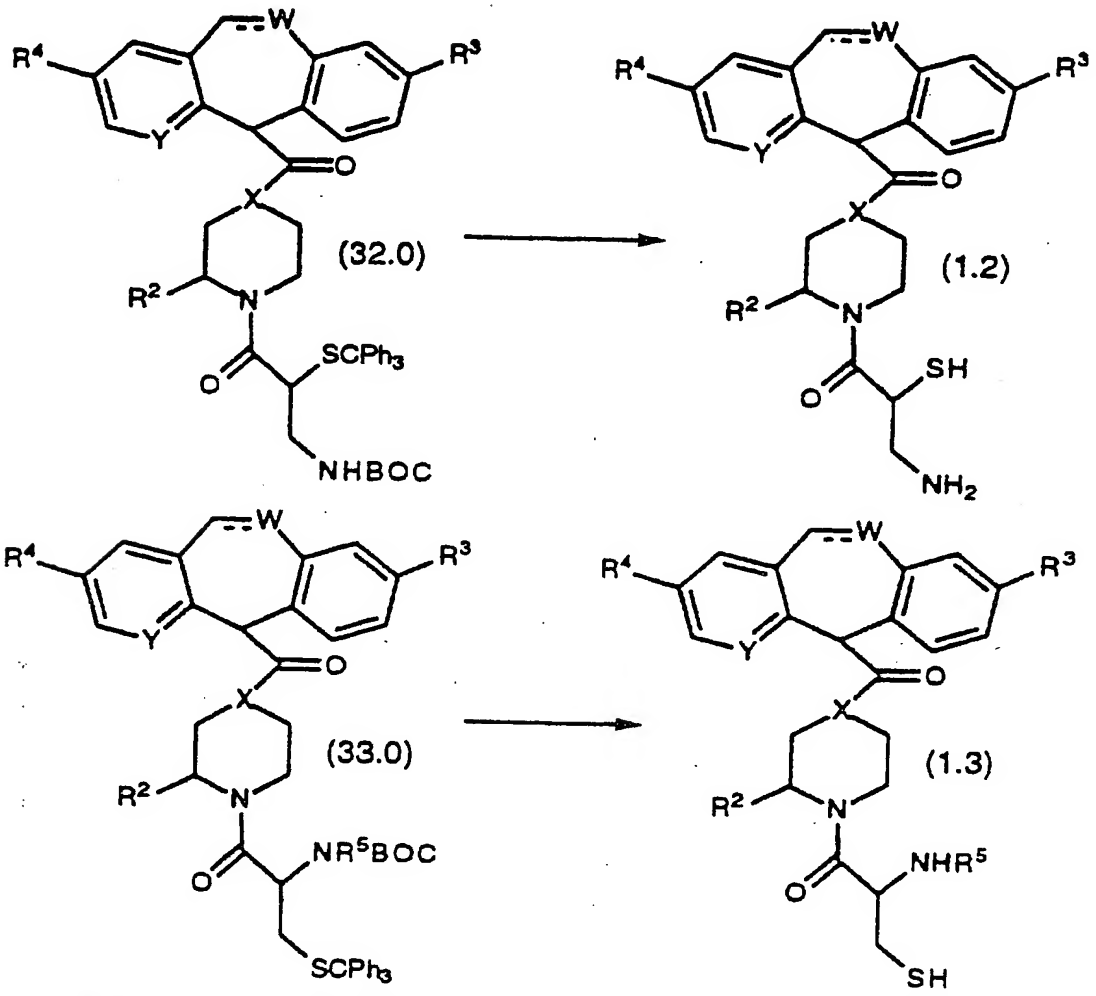
Compounds of Formula 1.0, wherein R^1 is a substituent (m) to (q) can be made by reacting a compound of Formula 10.1 or 30.0 with a pyridyl isocyanate, pyridyl N-oxide isocyanate or piperidyl isocyanate corresponding to the pyridyl, pyridyl N-oxide or piperidyl moiety, respectively, of the substituent groups (m) to (q). The reaction is carried out in a suitable solvent such as DMF, THF or chloroform using techniques well known in the art. Alternatively, these ureas can be prepared by reacting a compound of Formula 10.1 or 30.0 with phosgene to form a chloroformate intermediate (R^1 is -C(O)Cl). This chloroformate is generally not isolated, and is reacted with pyridyl amine, pyridyl N-oxide amine or piperidyl amine corresponding to the pyridyl, pyridyl N-oxide or piperidyl moiety, respectively, of the substituent groups (m) to (q) by techniques well known in the art.

Compounds of Formula 1.0 wherein R^1 is a substituent (r) to (v) can be made by reacting a compound of Formula 10.1 or 30.0 with a pyridyl chloroformate or piperidyl chloroformate; or, alternatively, reacting a compounds of Formulas 10.1 or 30.0 with excess phosgene and reacting the chloroformate thus produced with a hydroxypyridyl N-oxide or hydroxypiperidyl. The reaction is carried out in a suitable solvent, such as dichloromethane, in the presence of a tertiary amine, such as pyridine, by techniques well known in the art.

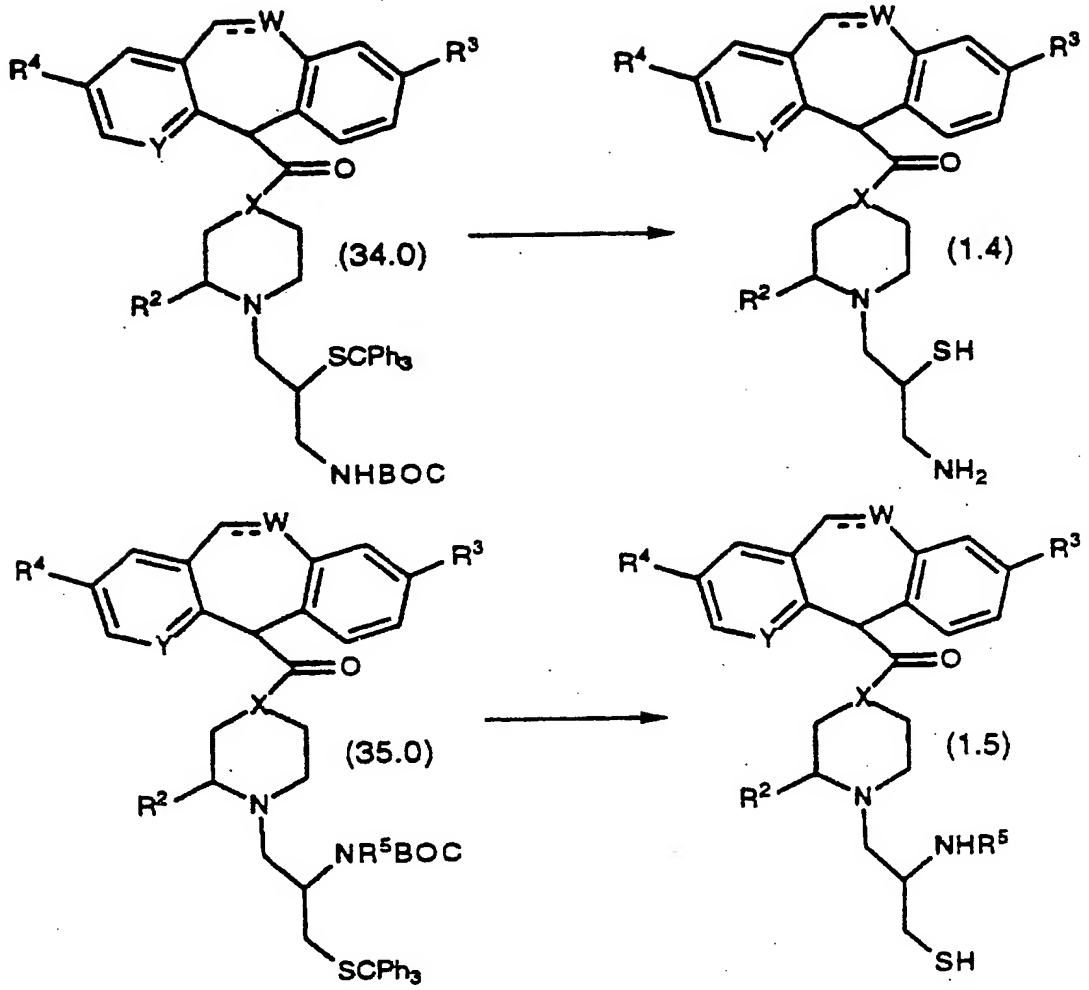
Reductive alkylation of the compound of Formula 10.1 or 30.0 is accomplished by reacting the compound of Formula 10.1 or 30.0 with an aldehyde in DMF with a dehydrating agent such as molecular sieves at room temperature (about 25°C). This reaction is followed by reduction of the intermediate imine with a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride. The reduction is usually carried out at room temperature in a suitable solvent such as DMF.

When compounds of Formulas 10.1 (X is N) or 30.0 (X is CH) are acylated to make the compounds of Formula 1.0 wherein R^1 is substituents (e) or (g), the protected compounds of Formulas 32.0 and 33.0, respectively are formed (CPh_3 represents triphenylmethyl). These protected compounds can be deprotected by using trifluoroacetic acid and triethylsilane to yield the compounds of Formulas 1.2 and 1.3, respectively. The compounds of Formulas 1.2 and 1.3 are isolated as the

hydrochloride salt following the procedure described in Example 1E WO95/00497.



When compounds of Formulas 10.1 (X is N) or 30.0 (X is CH) are reductively alkylated to make the compounds of Formula 1.0 wherein R^1 is substituents (f) or (h), the protected compounds of Formulas 34.0 and 35.0, resperctively are formed. These protected compounds can be deprotected by using trifluoroacetic acid and triethylsilane to yield the compounds of Formulas 1.4 and 1.5, respectively.



Certain compounds of Formula (1.0) can be converted to other compounds of the Formula (1.0) using standard reaction conditions. For example, compounds of the formula (1.0) wherein R^2 is $-CO_2H$, (i.e., $-C(O)OR^8$ and R^8 is H), can be prepared by ozonolysis of a compound of Formula (1.0) wherein R^2 is $CH_2=CH-$, followed by oxidation of the resulting aldehyde.

Compounds of the Formula (1.0) wherein R^2 is $-C(O)OR^8$, where R^8 is other than H, can be prepared from a compound of the formula (1.0) wherein R^2 is $-CO_2H$ by treating with $SOCl_2$ or oxalyl chloride, then with an alcohol of the formula R^8OH, wherein R^8 is as defined above. Similarly, compounds of formula (1.0) wherein R^2 is $-C(O)NR^8R^9$ can be prepared from a compound of the formula (1.0) wherein R^2 is $-CO_2H$ via essentially the same method but substituting and amine of the formula R^8R^9NH for the alcohol R^8OH. Alternatively, compounds of Formula (1.0) wherein R^2 is $-C(O)NR^8R^9$ can be prepared by reacting a compound of

the Formula (1.0) wherein R^2 is $-CO_2H$ with an amine R^8R^9NH in the presence of a coupling agent, such as DCC or DEC.

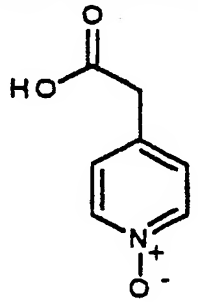
In an analogous manner, compounds of Formula (1.0) wherein R^2 is alkyl substituted by a group of the formula $-C(O)OR^8$ or $-C(O)NR^8R^9$ can be prepared via substantially the same procedures as described above to form compounds wherein R is $-CO_2H$, $-C(O)OR^8$ or $-C(O)NR^8R^9$, by replacing the compound of Formula (1.0) wherein R^2 is $CH_2=CH-$ with an appropriate alkenyl group, (i.e., a group of the formula $-(CH_2)_p-CH=CH_2$, wherein p is 1, 2, 3, 4, etc.).

Compounds of the Formula (1.0) wherein R^2 contains a substituent of formula $-S(O)_tR^8$, wherein t = 1 or 2, can be prepared by oxidation of an analogous compound of the formula (1.0) wherein R^2 contains a substituent of formula $-S(O)_tR^8$, wherein t = 0, using a suitable oxiding agent, such as a peracid, preferably MCPBA.

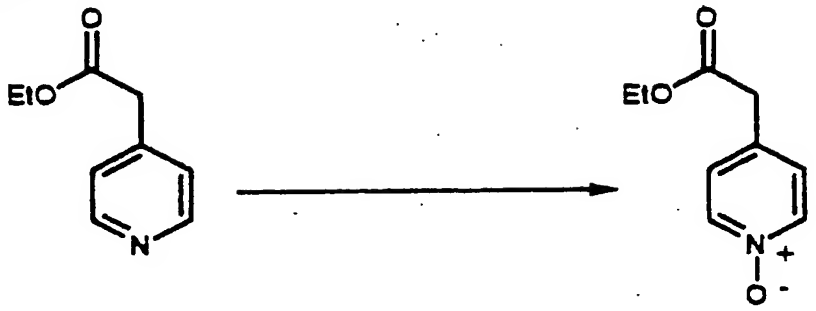
In the above processes, it is sometimes desirable and/or necessary to protect certain R^1, R^2, etc., groups during the reactions. Conventional protecting groups are operable as described in Greene, T.W., "Protective Groups In Organic Synthesis," John Wiley & Sons, New York, 1981, the disclosure of which is incorporated herein by reference thereto. For example, see Table 1 on page 60 of WO 95/10516 published April 20, 1995.

The compounds useful in this invention may be prepared by the methods disclosed in WO 95/10516, and by the methods described in the examples below. These examples should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to thosse skilled in the art.

PREPARATIVE EXAMPLE 1

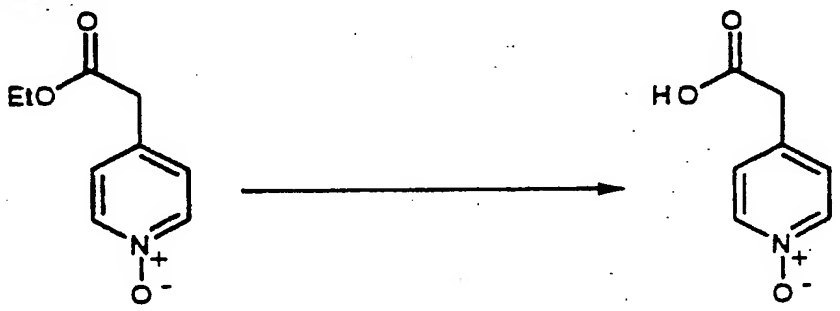


Step A:



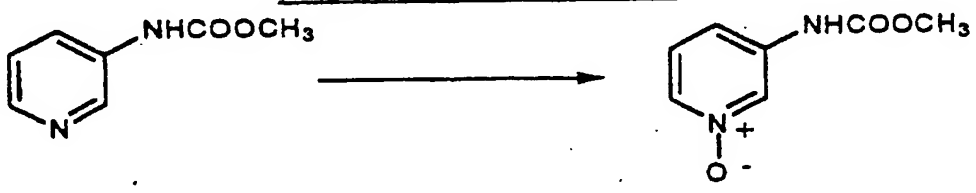
Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous) and then water. Dry over $MgSO_4$, concentrate *in vacuo* to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/CH_2Cl_2)to give 8.12 g of the product compound (Et represents -C_2H_5 in the formula). Mass Spec.: MH^+ = 182.15

Step B:



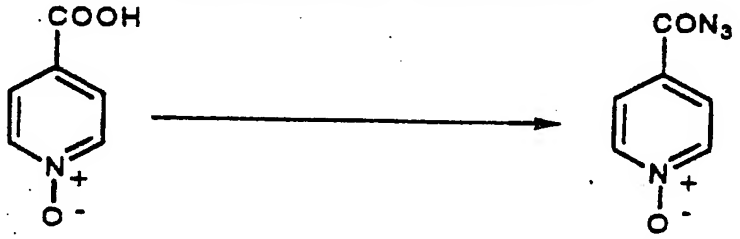
Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of ethanol and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry ethanol, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 2



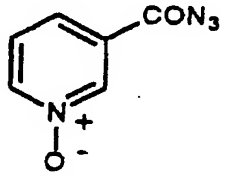
Combine 10 g (65.7 mmol) of 3-methoxycarbonylaminopyridine and 150 mL of CH_2Cl_2, cool to 0°C and slowly add (dropwise) a solution of 13.61 g (78.84 mmol) of MCPBA in 120 mL of CH_2Cl_2 at 0°C over a period of 1 hour. Stir the mixture at 25°C for 5 days, then wash with saturated $NaHCO_3$ (aqueous), then water and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give the product compound. Mass Spec.: MH^+ = 169

PREPARATIVE EXAMPLE 3



Combine 5 g (36.0 mmol) of isonicotinic acid 1-N-oxide and 150 mL of anhydrous DMF, add 5.5 mL (39.6 mmol) of triethylamine and stir at 0°C for 0.5 hours. Slowly add (dropwise) 8.5 mL (39.6 mmol) of diphenylphosphoryl azide at 0°C over 10 minutes, stir at 0°C for 1 hour and then at 25°C for 24 hours (as generally described in Pavia, *et al.*, Journal of Medicinal Chemistry, 33, 854-861 (1990). Concentrate *in vacuo* to a residue and chromatograph (silica gel, 0.5%-1% MeOH/CH_2Cl_2) to give 5.9 g of the product compound.

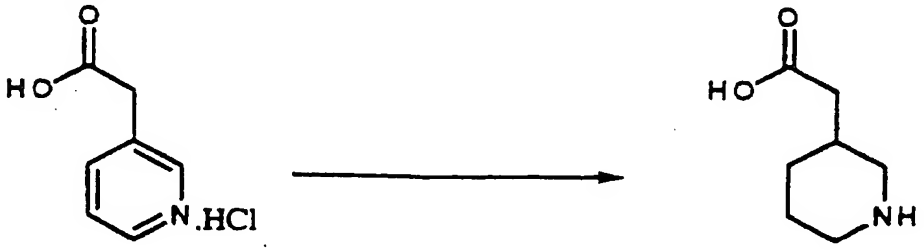
Using nicotinic acid 1-N-oxide and substantially the same procedure as described for Preparative Example 3 the following compound was prepared:



(3A)

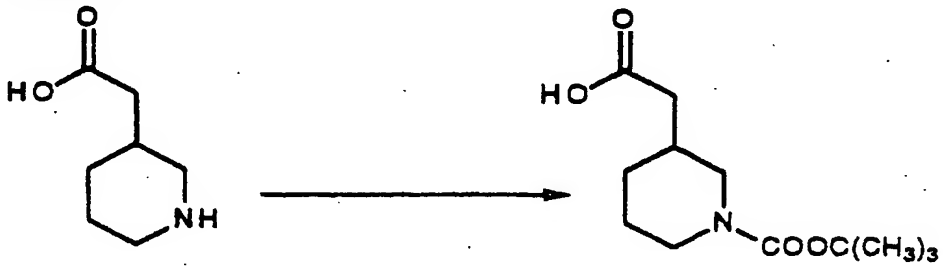
PREPARATIVE EXAMPLE 4

Step A:



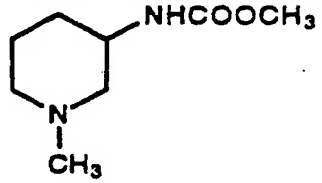
Hydrogenate 25 g (144 mmol) of 3-pyridylacetic acid hydrochloride for 144 hours using the procedure described in Preparative Example 17, Step A, of WO 95/10516, to give 20 g of the product compound. Mass Spec.: $MH^+ = 144$.

Step B:



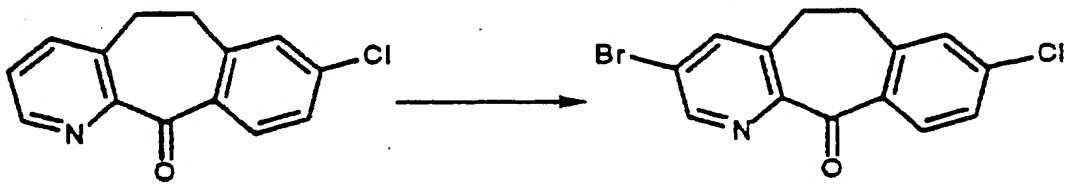
React 12 g (83.8 mmol) of the product of Step B for 148 hours using the procedure described in Preparative Example 17, Step D, of WO 95/10516, to give 17.5 g of the product compound. Mass Spec.: $MH^+ = 244.25$

PREPARATIVE EXAMPLE 5



Combine 25 g (164.4 mmol) of methyl 3-pyridylcarbamate and 163.3 mL of 1N HCl (aqueous), stir until all of the solid dissolves, then hydrogenate over 10% Pd/C at 25°C at 55 psi for 220 hours. Filter, wash the solids with water and treat the combined filtrates with 150 mL of BioRad AG1X8 ion exchange resin (OH^-). Filter, wash the resin with water and concentrate the filtrate to a volume of 100 mL. Add 16.43 mL (197.3 mmol) of 37% formalin and hydrogenate over 10% Pd/C at 25°C at 55 psi for 89 hours. Filter, wash the solids with water and concentrate *in vacuo* to give 24.3 g of the title compound. Mass Spec.: $MH^+ = 173.2$

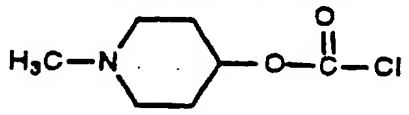
PREPARATIVE EXAMPLE 6



Cool 50.0 g (20.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C, slowly add 75 mL (93.69 mmol) of sulfur monochloride over 20 minutes, then slowly add 25

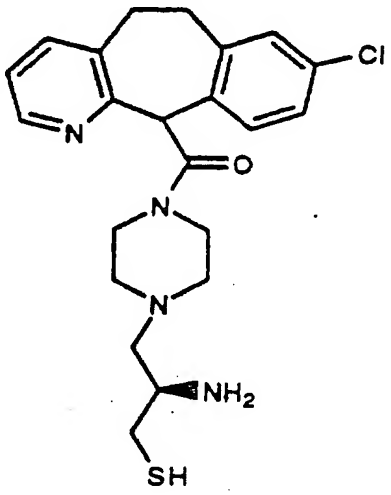
mL (48.59 mmol) of Br_2 over 15. Heat at 95°C for 20 hour, add 12.5 mL (24.3 mmol) of Br_2 and heat for a another 24 hours. Cool the mixture, and slowly add to a mixture of CH_2Cl_2 and 1N NaOH (aqueous) at 0°C. Wash the organic phase with water, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2 then 0.2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2), then chromatograph again (silica gel, 3%-8.5% EtOAc/hexane) to give 8.66 g of the product compound. Mass Spec.: $MH^+ = 322$

PREPARATIVE EXAMPLE 7

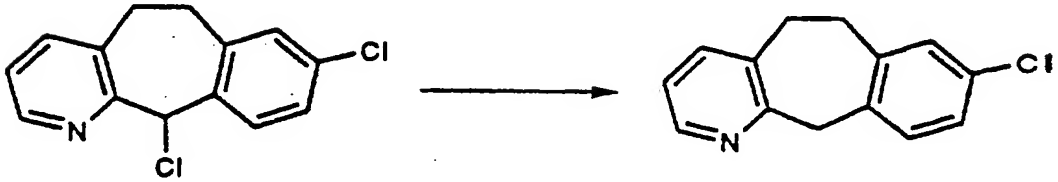


Combine 10 mL of dry CH_2Cl_2 and 914.6 mL (28.1 mmol) of a 1.93M solution of phosgene in toluene, cool to 0°C and slowly add (dropwise) a solution of 0.6484 g (5.62 mmol) of 4-hydroxy-1-N-methylpiperidine, 1.214 mL (15 mmol) of pyridine and 10 mL of dry CH_2Cl_2 over 10 minutes, then stir at 0° to 25°C for 2 hours. Purge excess phosgene with N_2 then concentrate in vacuo to give the title compound.

EXAMPLE 1



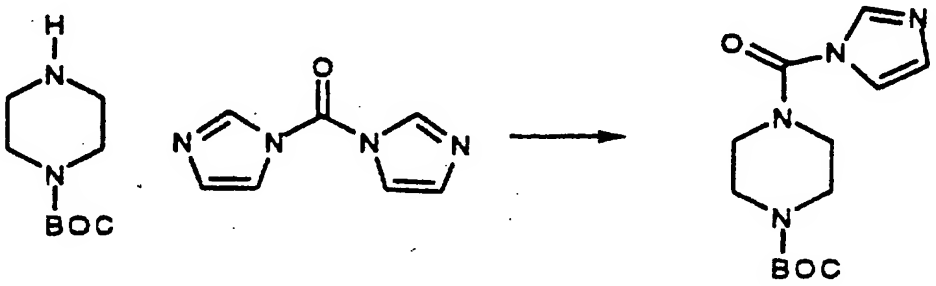
Step A:



Following the procedure of Villani et al., J. Med. Chem. 15, 750 (1972), the product of Preparative Example 2 was dissolved in acetic acid

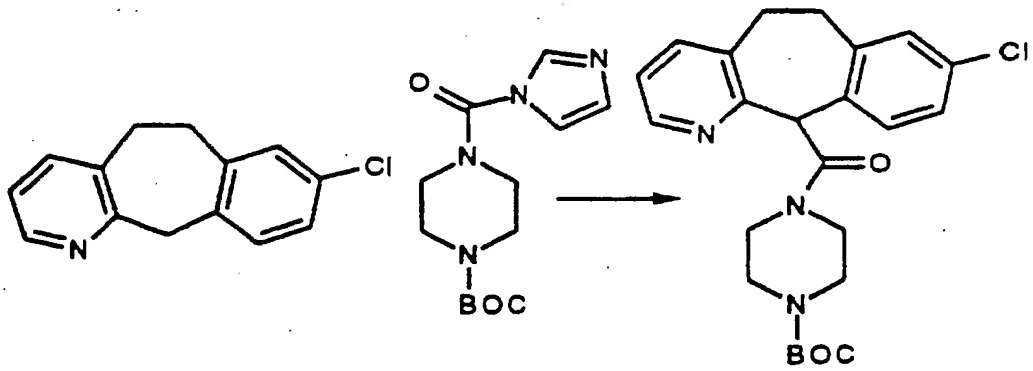
and excess zinc was added. This mixture was heated for two hours at 80°C. The reaction mixture was filtered and concentrated under vacuo. Aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate, filtered and concentrated under vacuo. The concentrated material was chromatographed on silica gel using ethyl acetate-hexane to obtain the product.

Step B:



Piperazine protected with a BOC group (commercially available) was dissolved in methylene chloride and 1.2 equivalents of carbonyl-diimidazole was added at 0°C and the mixture was stirred for 15 minutes. Sodium chloride solution was added and the mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuo to obtain the product.

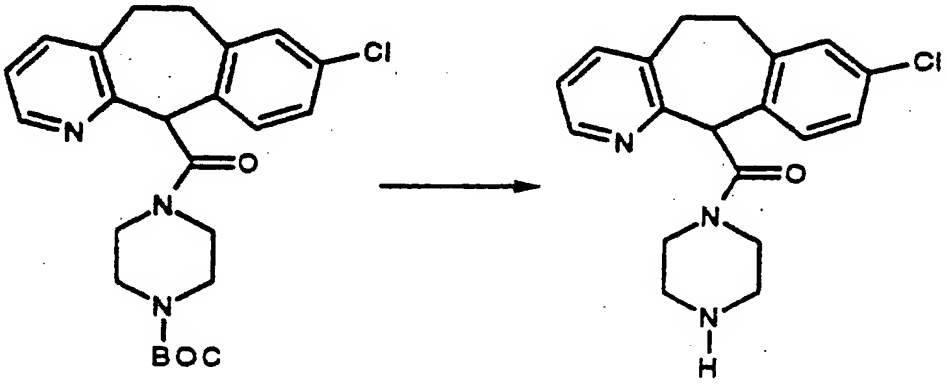
Step C:



The product of Step A was dissolved in tetrahydrofuran and cooled to -78°C. One equivalent of butyl lithium was added and the mixture was stirred for 10 minutes. One equivalent of the product of Step B in tetrahydrofuran was added and the mixture was stirred for 1 hour at -78°C, and then at 25°C for 18 hours. Water was added and the mixture was extracted with ethyl acetate, the organic layer was dried over magnesium sulfate and concentrated under vacuo. The concentrated material was

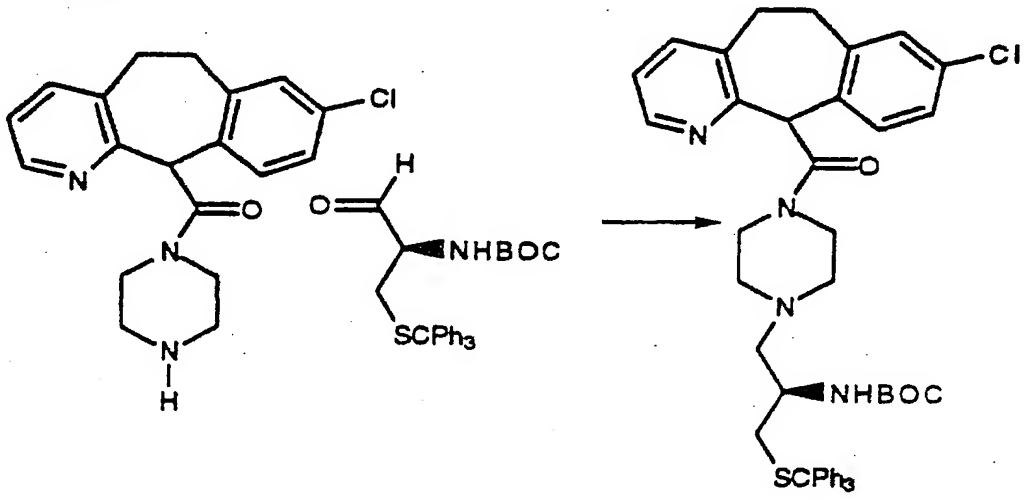
chromatographed on silica gel using ethyl acetate-hexane to give the product as a tan solid, M+1=442.

Step D:



The product of Step C was dissolved in HCl-Dioxane and stirred until reaction was completed (about 1 hour). Concentration in vacuo gave the product.

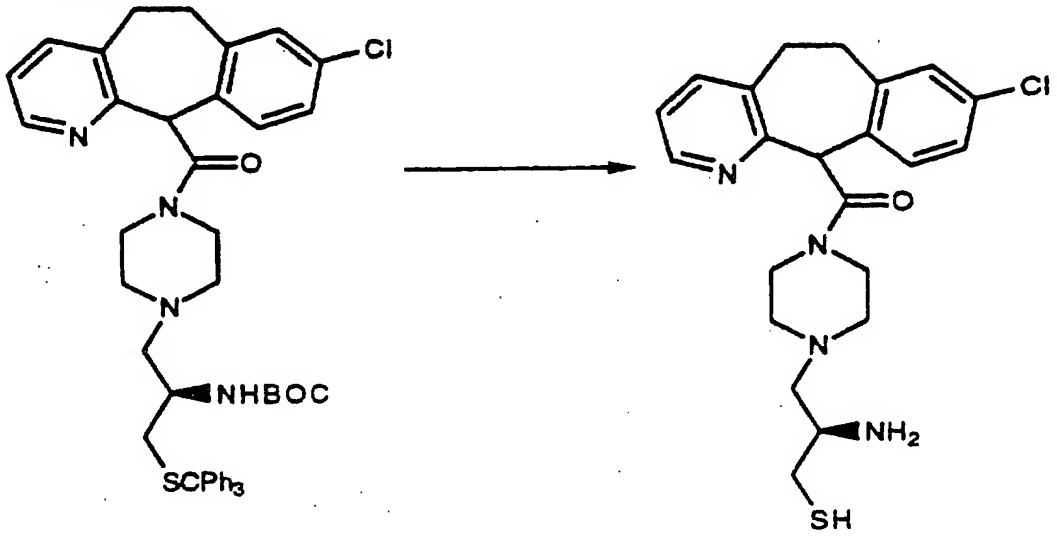
Step E:



The product of Step D was dissolved in N,N-dimethylformamide and the pH was adjusted to 6 with triethylamine. Sodium triacetoxyborohydride, 1.25 equivalents, and crushed 4A molecular sieves were added to the solution. The resulting mixture was cooled to 0°C under nitrogen and 1.5 equivalents of the reactant aldehyde (see Example 1 on page 45 of WO95/00497) in N,N-dimethylformamide was added dropwise. After addition was completed, the mixture was stirred at 0°C for 2 1/2 hours. The mixture was then diluted with ethyl acetate, filtered, and washed with sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuo. The

concentrated material was chromatographed on silica gel using ethyl acetate-hexane to give a white solid. M + 1 = 772.

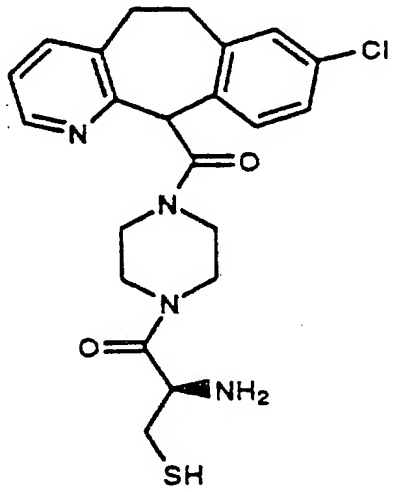
Step E:



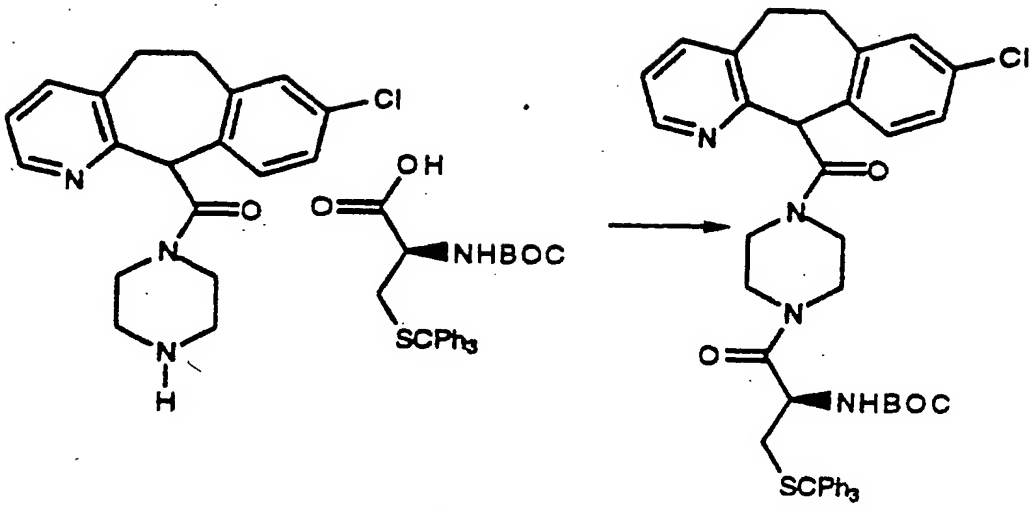
The product of Step E was treated with 1N HCl in acetic acid at room temperature for 1/2 hour, then at 47°C for 15 minutes, cooled to 20°C and treated with triethylsilane for 1/2 hour. The hydrochloride of the tiltle compound was isolated as a white powder by diluting the reaction mixture with ethyl acetate followed by centrifugation. M + 1 = 431.

EXAMPLE 2

If one were to follow the procedures described in Steps A and B then one would obtain a compound of the formula:

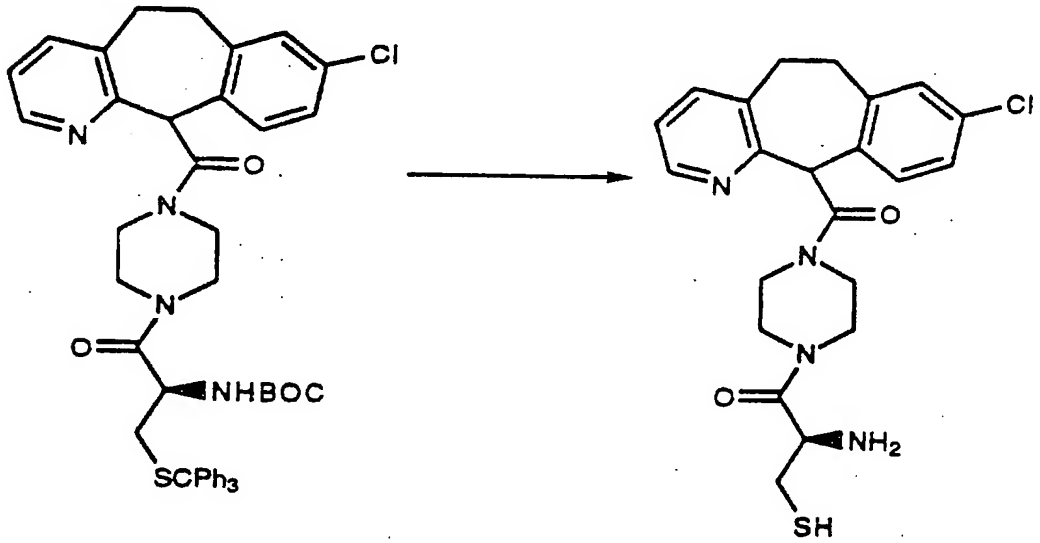


Step A:



Dissolve the product of Example 1, Step D, in N,N-dimethylformamide and add 1 equivalent of the reactant carboxylic acid (commercially available), 1 equivalent of 1-hydroxybenzotriazole, 1 equivalent of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (DEC) and 1 equivalent of triethylamine. Stir until reaction is complete, about 18 hours. Concentrate in vacuo. Chromatograph on silica gel using ethyl acetate-hexane to obtain the product.

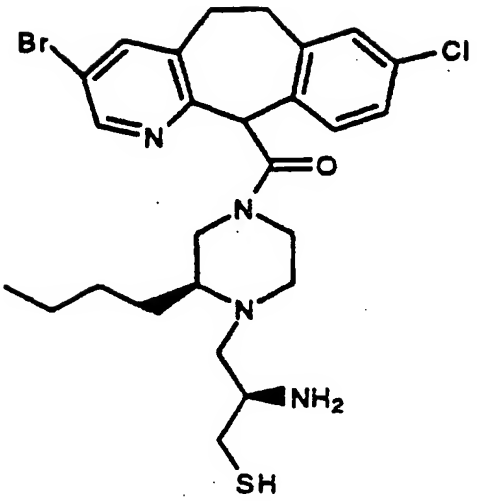
Step B:



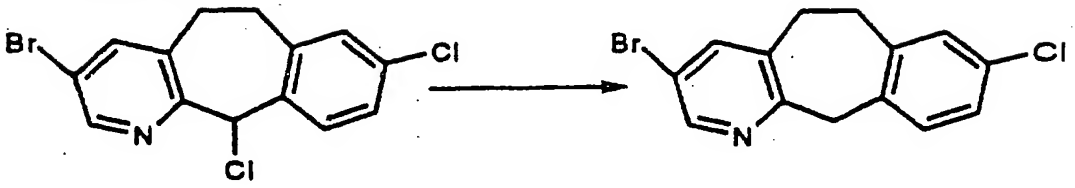
React and purify as in Example 1, Step F, to obtain the product.

EXAMPLE 3

If one were to follow the procedures described in Steps A to F then one would obtain a compound of the formula:

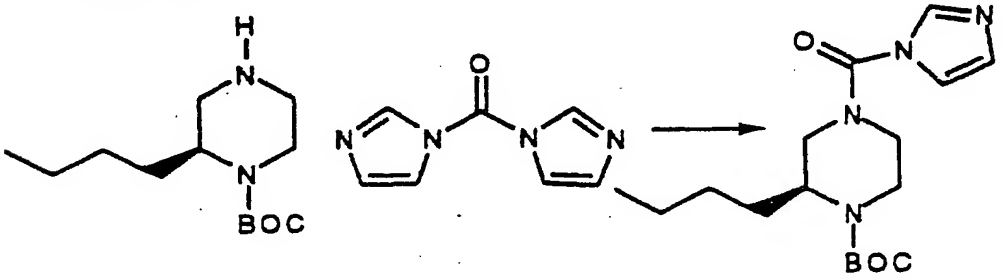


Step A:



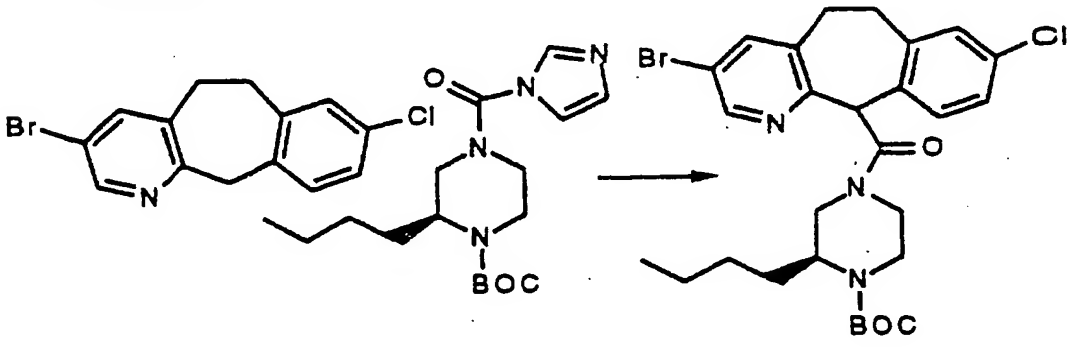
Follow the procedure set forth in Example 1, Step A, using the product of Preparative Example 10 to obtain the product.

Step B:



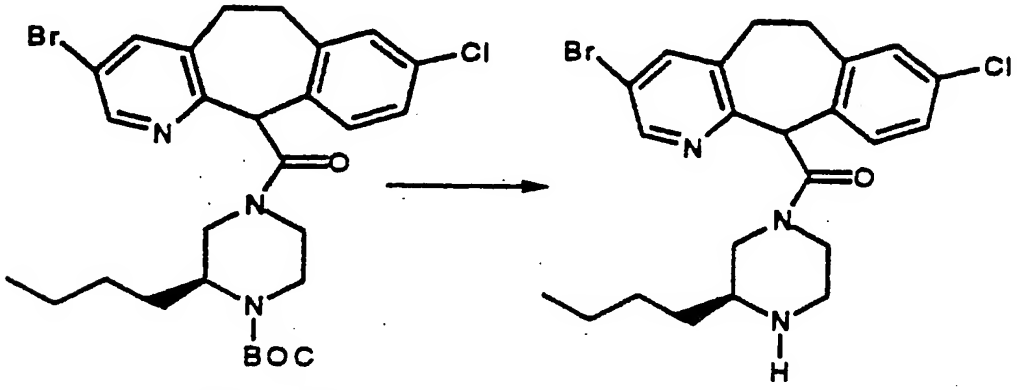
Follow the procedure of Example 1, Step B, using the product of Example 3, Step B, to obtain the product.

Step C:



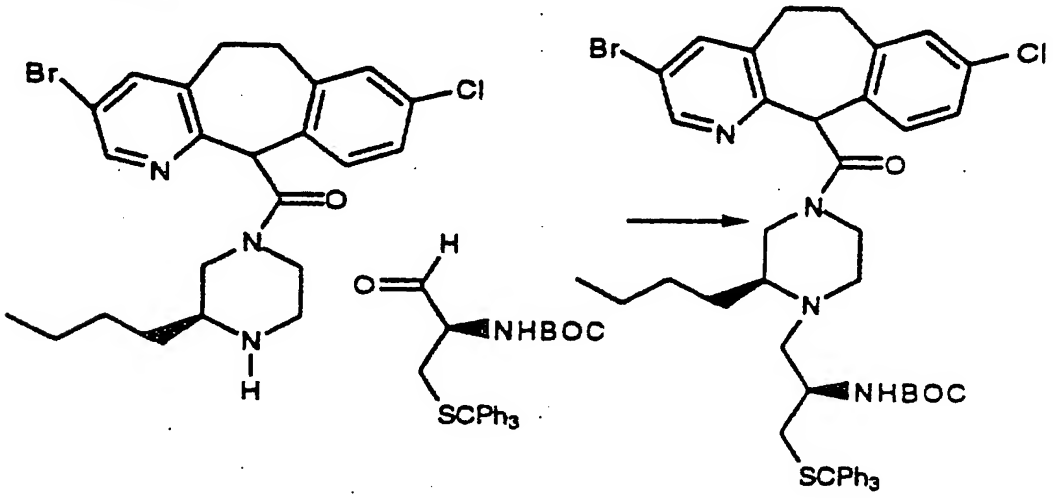
Follow the procedure of Example 1, Step C, using the products of Example 3, Steps A and B, to obtain the product.

Step D:



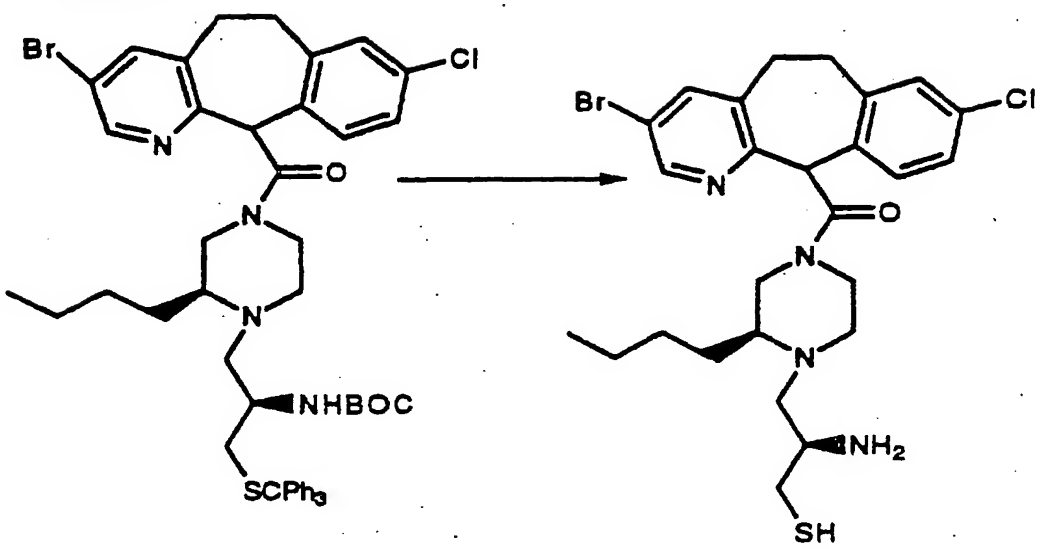
Follow the procedure of Example 1, Step D, using the product of Example 3, Step C, to obtain the product.

Step E:



Follow the procedure of Example 1, Step E, using the product of Example 3, Step D, and the aldehyde to give the product.

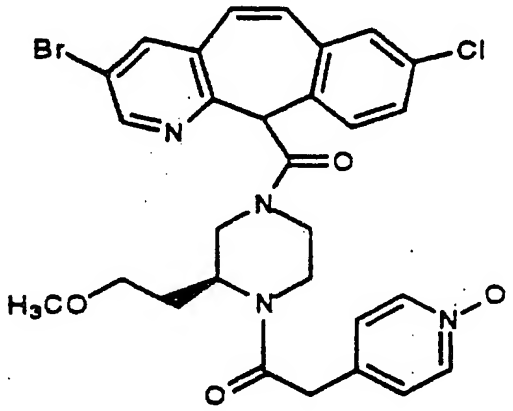
Step F:



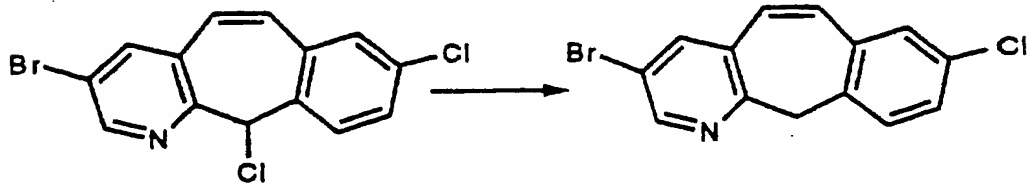
Follow the procedure of Example 1, Step F, using the product of Example 3, Step E, to give the product.

EXAMPLE 4

If one were to follow the procedures described in Steps A to E then one would obtain a compound of the formula:

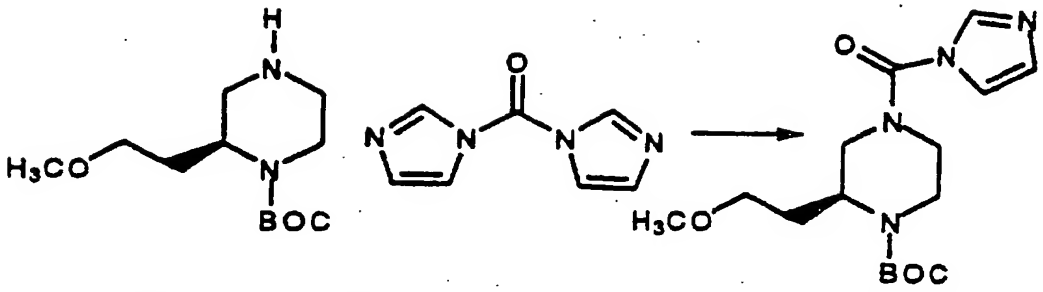


Step A:



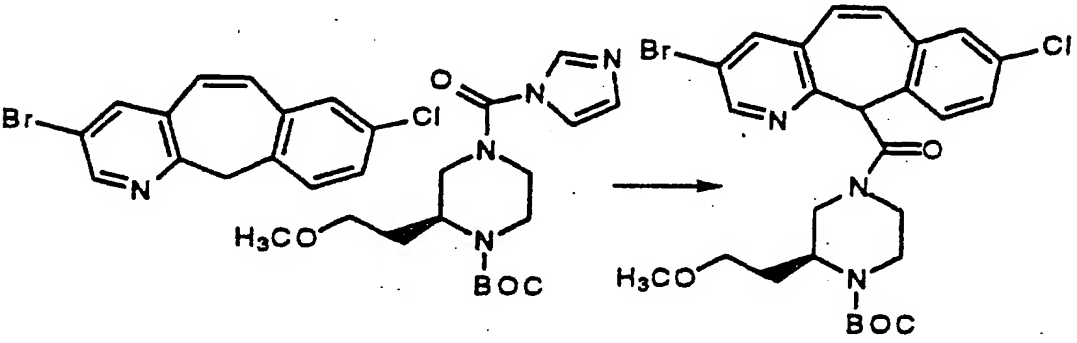
Follow the procedure of Example 1, Step A, using the product of Preparative Example 9 to obtain the product.

Step B:



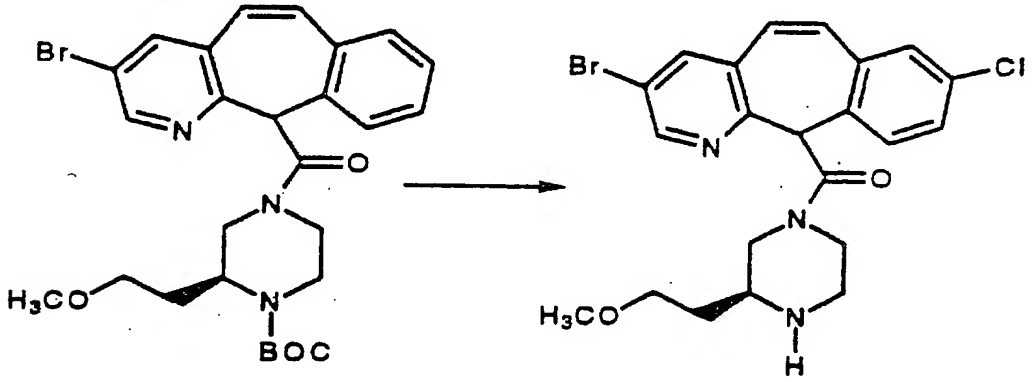
Follow the procedure of Example 1, Step B, to obtain the product.

Step C:



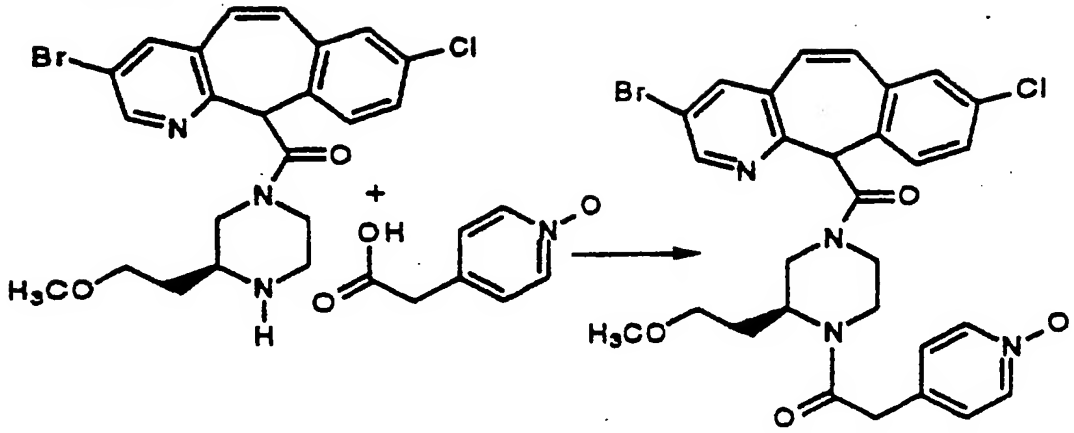
Follow the procedure of Example 1, Step C, using the products of Example 4, Steps A and B,to obtain the product.

Step D:



Follow the procedure of Example 1, Step D, using the product of Example 4, Step C, to obtain the product.

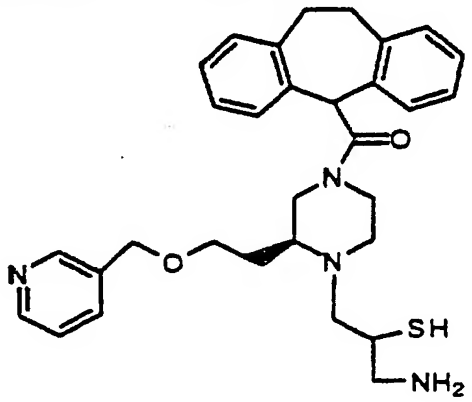
Step E:



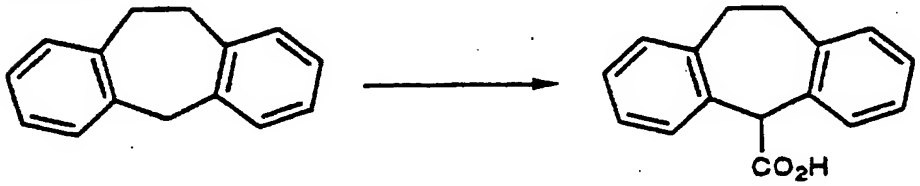
Follow the procedure of Example 2, Step A, using the product of Example 4, Step D, and Preparative Example 11, to obtain the product.

EXAMPLE 5

If one were to follow the procedures described in Steps A to F then one would obtain a compound of the formula:



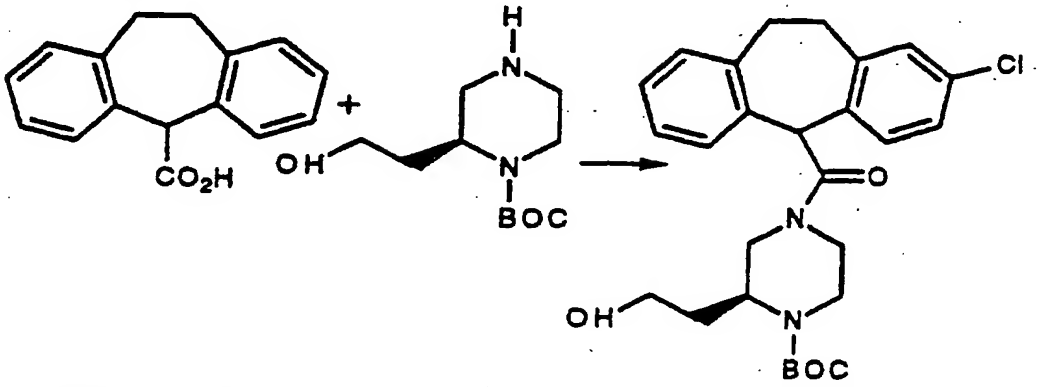
Step A:



Dibenzosuberane was dissolved in tetrahydrofuran and cooled to 0°C under nitrogen. 1.5 Equivalents of n-butyl lithium was added and allowed to warm to 20°C, and was kept at 20°C for 1 hour. The reaction mixture was poured onto crushed solid carbon dioxide. After 0.5 hours 10% aqueous hydrochloric acid was added and the mixture was extracted with methylene chloride. The organic layer was extracted with 0.1 M sodium hydroxide. The aqueous layer was cooled and the pH was

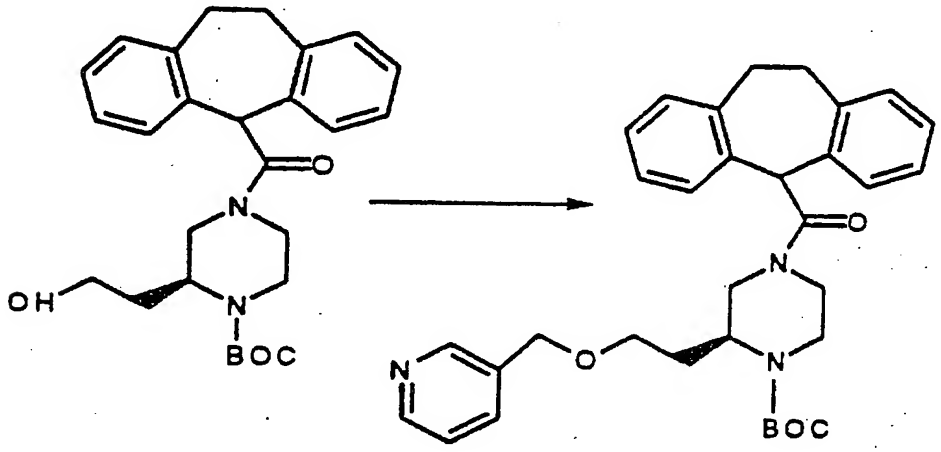
adjusted to 2 with 12 M hydrochloric acid. The precipitated product was filtered and dried giving a white solid.

Step B:



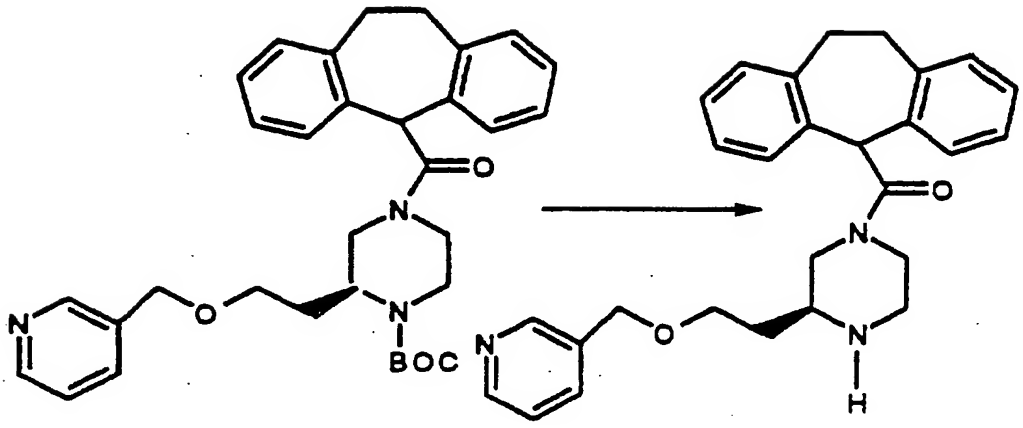
Make the piperazine reactant according to the procedure in Example 13 of WO95/00497. Follow the procudure of Example 2, Step A, above, to obtain the product.

Step C:



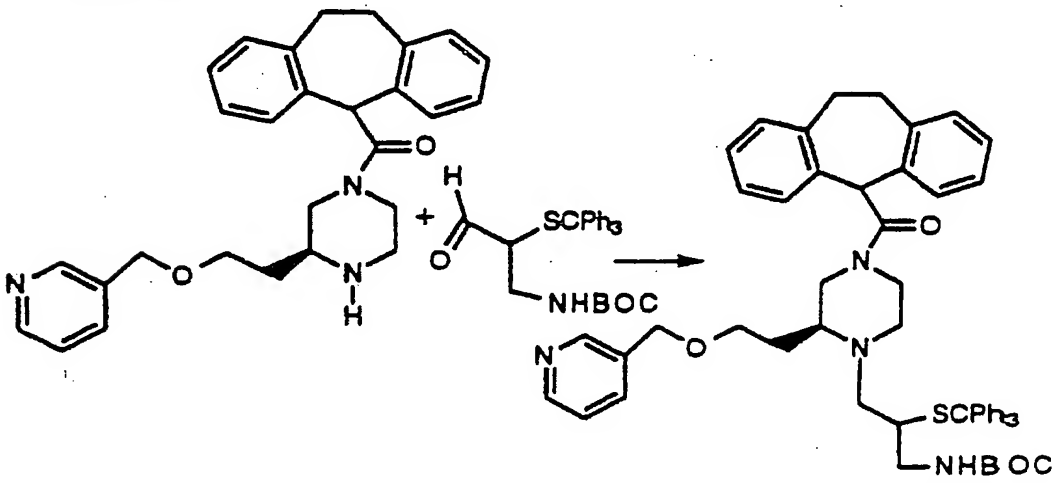
Dissolve the product of Step B in dry, degassed N,N-dimethyl-foramide and cool to 0°C. Add 1.3 equivalents of sodium hydride followed by 1.4 equivalents of 3-chloromethylpyridine. After 3 hours quench the reaction with saturated amonium chloride solution. Concentrate under vacuo and partition between ethyl acetate and sodium bicarbonate solution. Dry the organic layer over magnesium sulfate, filter and concentrate under vacuo. Chromatograph the residue on silica gel using ethyl acetate-hexane.

Step D:



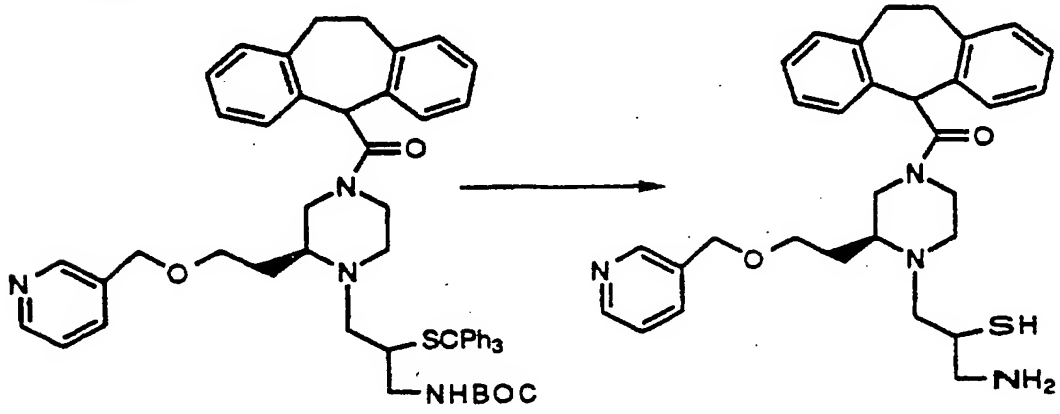
Follow the procedure of Example 1, Step D, to obtain the product.

Step E:



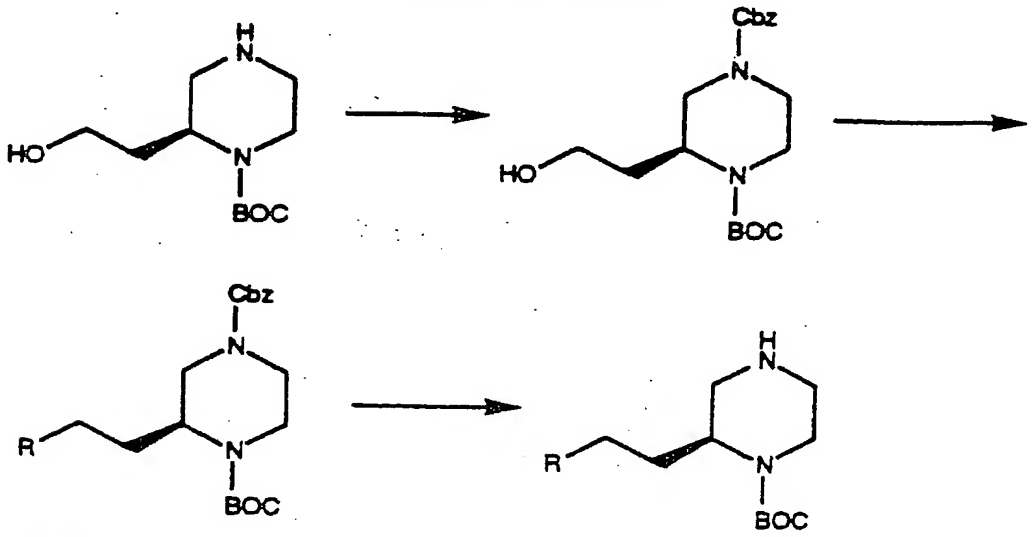
Prepare the reactant aldehyde by procedures similar to those described in Example 1 of WO95/00497. Follow the procedure of Example 1, Step E, above to obtain the product.

Step F:



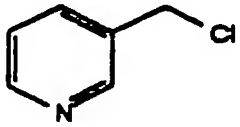
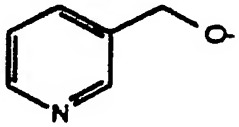
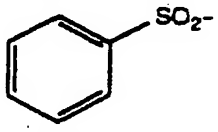
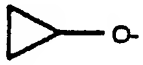
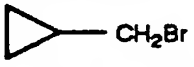
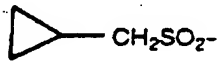
Follow the procedure of Example 1, Step F, to obtain the product.

EXAMPLES 6-10

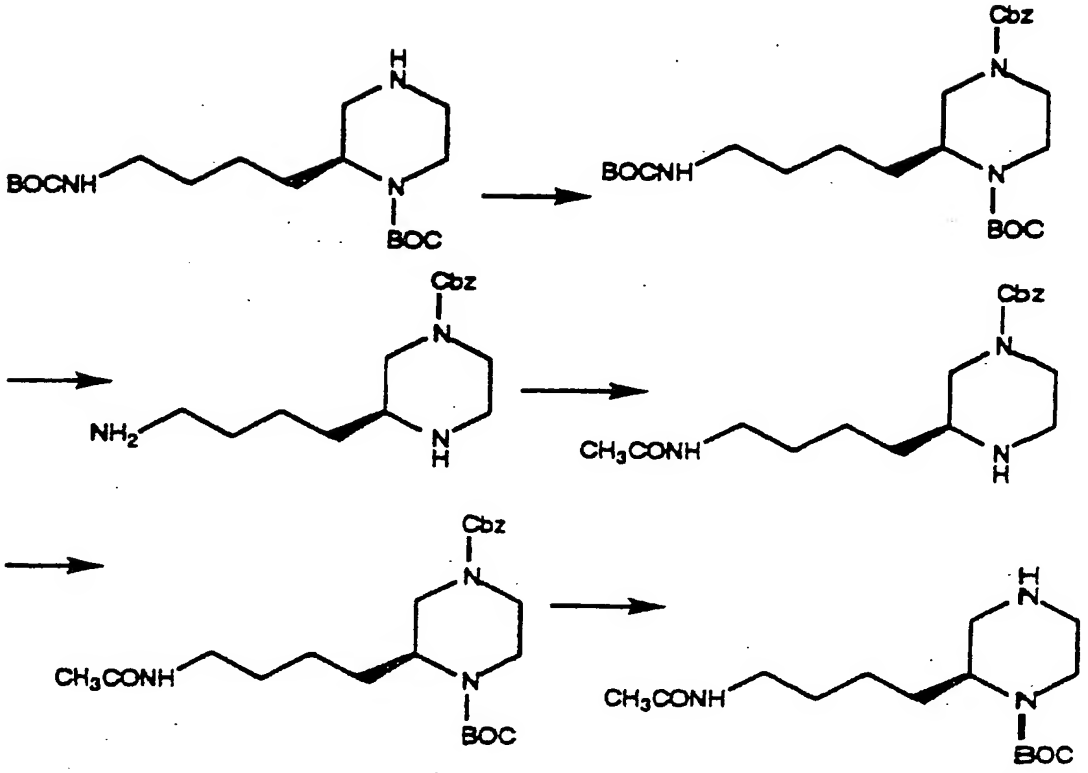


React the title compound of Example 13A of WO 95/00497 with benzyloxycarbonyl chloride according to standard conditions well known in the art, to obtain the N-Cbz (benzyloxycarbonyl) protected alcohol shown above. Purification of the protected alcohol, according to procedures well known in the art, and then reaction of the protected alcohol with the reagents in Column 1 of Table 1 would give the corresponding N-Cbz protected intermediates having R as defined in Column 2 of Table 1. After purification according to techniques well known in the art, the protected intermediate may be selectively deprotected (to remove the Cbz group) using mild catalytic hydrogenation procedures well known in the art. Following deprotection, purification by known techniques would yield the BOC-protected intermediate having the R group shown in Column 2 of Table 1.

TABLE 1

Column 1 - (Reagents)	Column 2 - R Group
 and NaH	Example 6  Prepare as described in Example 14 of WO 95/00497.
$C_6H_5SSC_6H_5$ + $(n\text{-}Bu)_3P$	Example 7  Prepare as described in Example 20B and 20C of WO 95/00497.
(i)  + $Hg(OAc)_2$ + CH_3COOH (ii) CH_2I_2 + Et_2Zn	Example 8  Prepare as described in Examples 26A and 26B of WO 95/00497.
(i) EtOCON=NCOOEt + $(C_6H_5)_3P$ + CH_3COSH (ii) NH_3 + CH_3OH +  (iii) Mg monoperphthalic acid + CH_3OH	Example 9  Prepare as described in Examples 29A, 29B and 29C of WO 95/00497.
n-C_3H_7I + NaH	Example 10 n-C_3H_7O- Prepare as described in Example 13C of WO 95/00497.

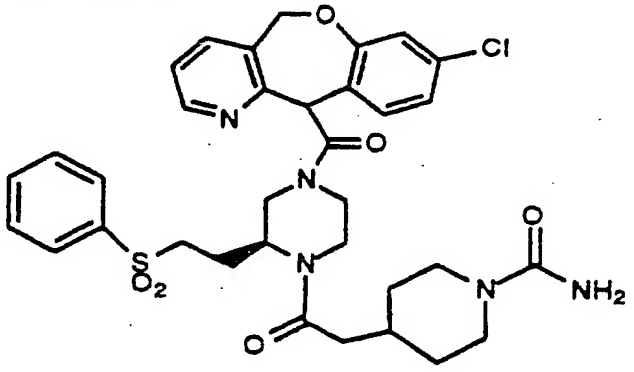
EXAMPLE 11



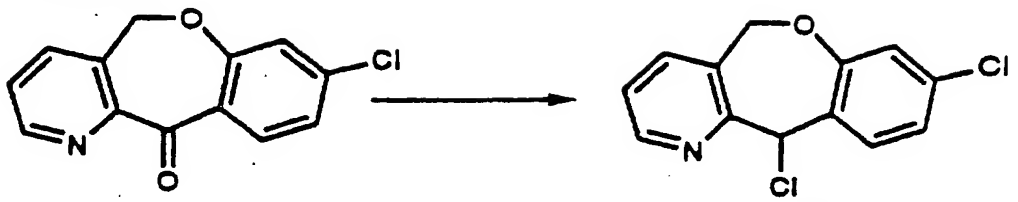
Convert the title compound from Example 27D of WO 95/00497, by the scheme shown above, using procedures well known in the art, into 1-*tert*-butoxycarbonyl-2(S)-(4-acetylaminobutyl)piperazine.

EXAMPLE 12

If one were to follow the procedures in Steps A to G, then one would obtain the compound:

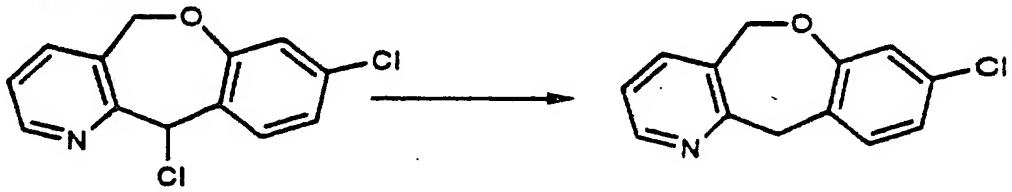


Step A:



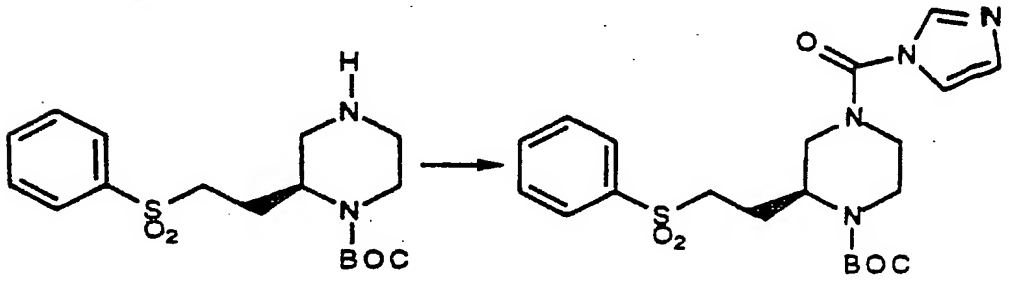
Prepare the starting material according to the procedure described in Example 4C of WO89/10369. Convert the starting material into the chloro product by the method described in U.S. 3,409,621.

Step B:



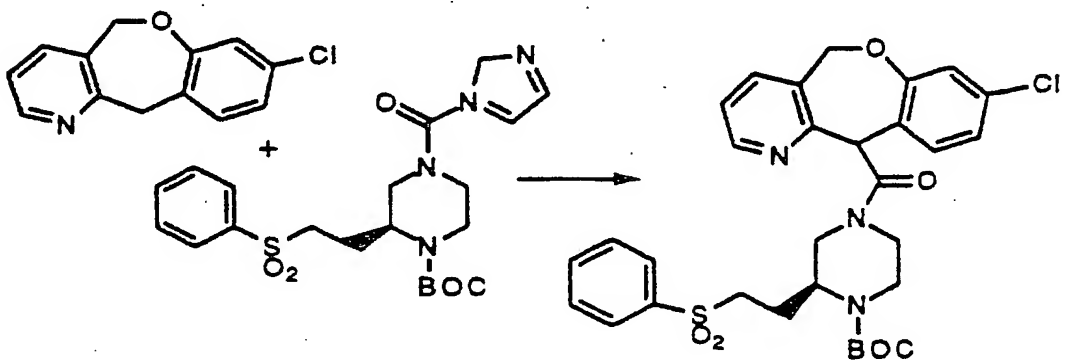
Follow the procedure in Example 1, Step A, to obtain the product.

Step C:



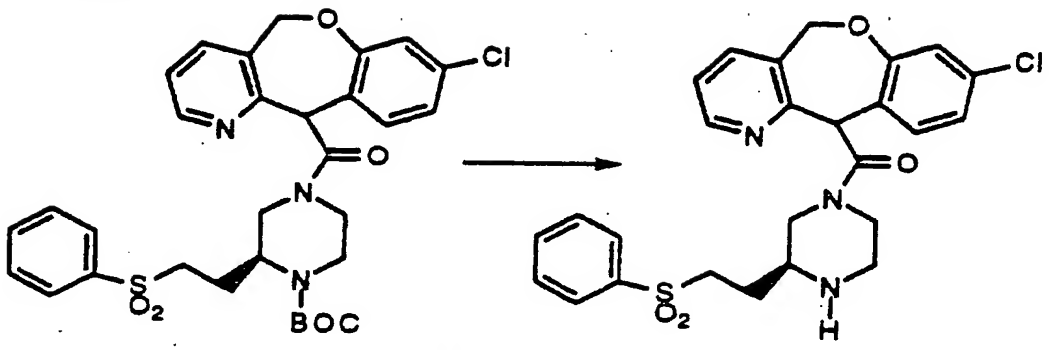
React the product of Step A with the product of Example 7 by the method of Example 1, Step B, to obtain the product.

Step D:



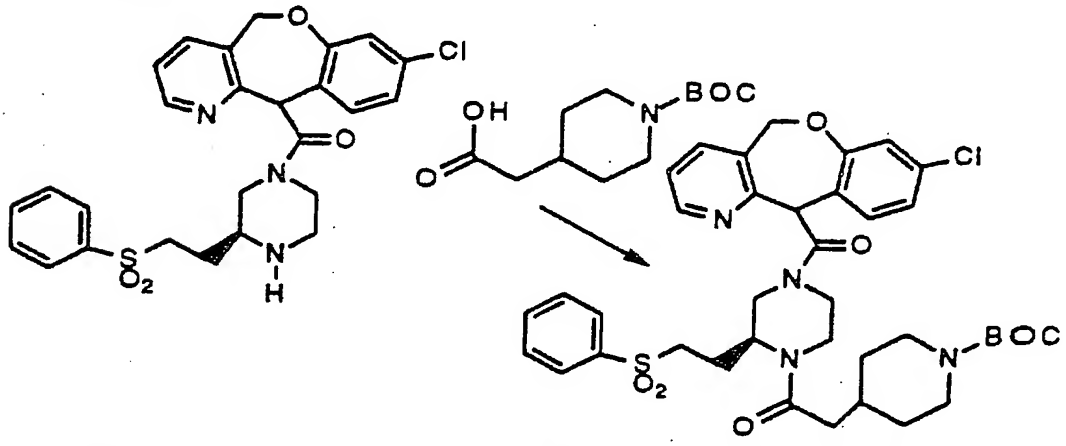
Follow the procedure in Example 1, Step C, to obtain the product.

Step E:



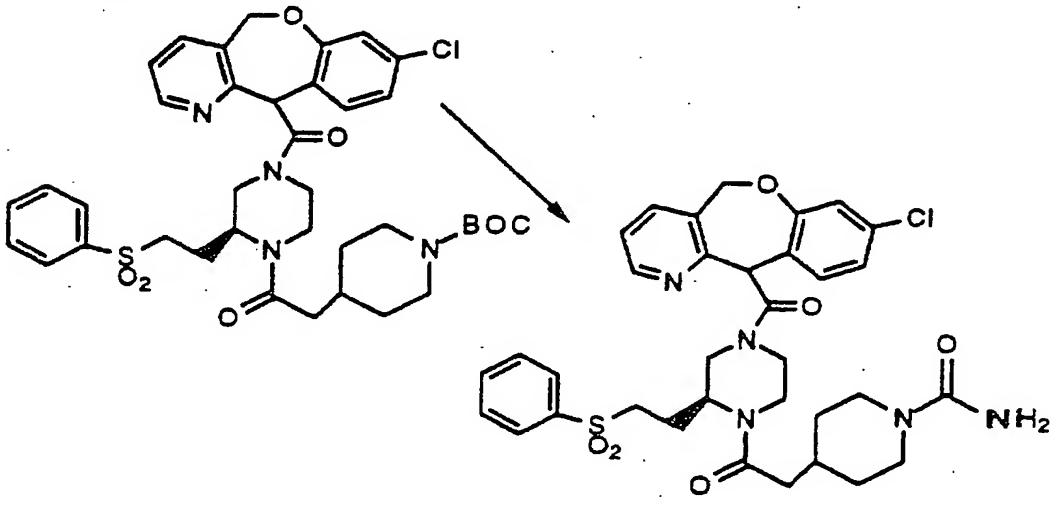
Follow the procedure in Example 1, Step D, to obtain the product.

Step F:



React the product of Example 12, Step E, with the BOC protected 4-piperidinylacetic acid of Preparative Example 5D, according to the procedure in Example 2, Step A, to obtain the product.

Step G:

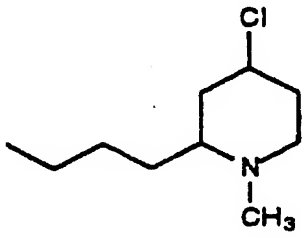


Dissolve the product of Step F in HCl-Dioxane and stir for 1 hour. Concentrate in vacuo. Partition between sodium bicarbonate solution and

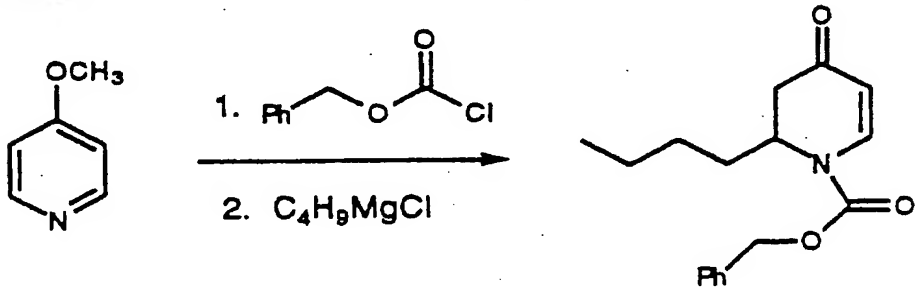
ethyl acetate. Dry the organic layer over magnesium sulfate, filter and concentrate under vacuo. Dissolve the residue in methylene chloride and add excess trimethylsilylisocyanate. Stir under nitrogen for 18 hours. Add additional trimethylsilylisocyanate and stir until the reaction is complete. Wash with aqueous sodium bicarbonate solution. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo. Chromatograph the residue on silica gel using methanol-methylene chloride to give the product.

EXAMPLE 13

If one were to follow the procedures in Steps A to E, then one would obtain the compound:

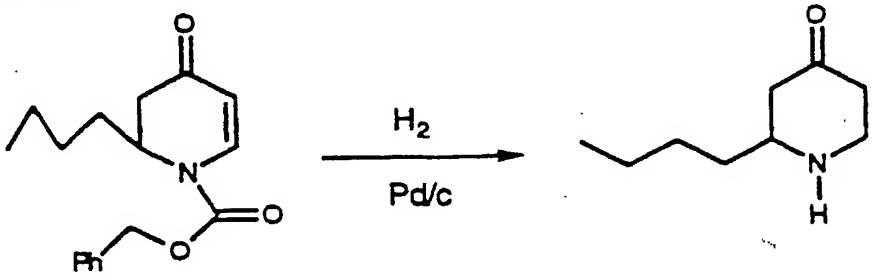


Step A:



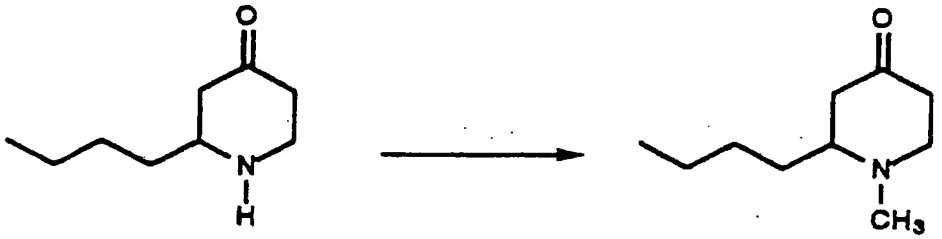
According to the procedure of D.L. Comins, et al., in Tet. Lett., 4549 (1986), dissolve 4-methoxypyridine in THF and cool to -23°C. Add benzylchloroformate dropwise (1 equivalent) followed by 1 equivalent of butyl magnesium chloride in THF added dropwise. Pour into 10% hydrochloric acid and extract with ether. Dry over $MgSO_4$ and concentrate. (Ph in the above formula represents phenyl).

Step B:



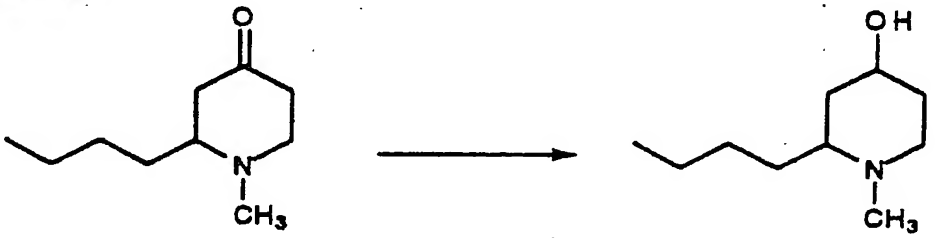
Dissolve the product of Step A in ethanol containing 10% palladium on carbon and hydrogenate at 60 psi. Filter and concentrate under vacuo to obtain the product.

Step C:



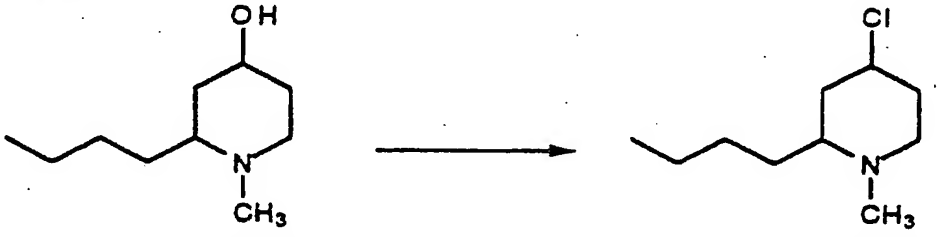
Dissolve the product of Step B in tetrahydrofuran, cool to 0°C under nitrogen and add one equivalent of sodium hydride. After stirring for 15 minutes, one equivalent of methyl iodide is added. Stir the reaction for 15 minutes, concentrate under vacuo and chromatograph on silica gel using methanol-methylene chloride.

Step D:



Dissolve the product of Step C in ethanol and add an excess of sodium borohydride. Concentrate under vacuo. Partition between water and ethyl acetate. Dry the organic layer over magnesium sulfate, filter and concentrate under vacuo.

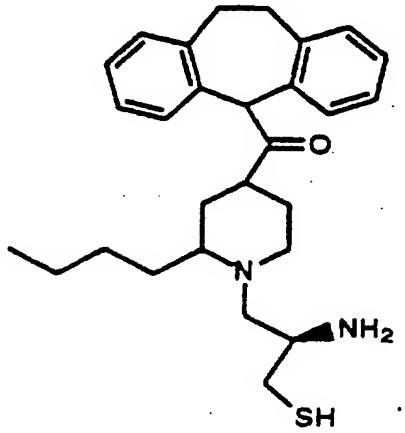
Step E:



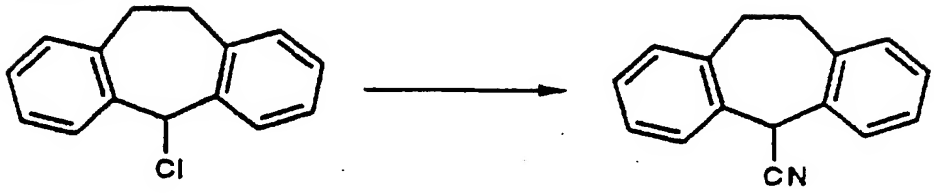
Dissolve the product of Step D in pyridine containing an excess of thionyl chloride. Stir for 18 hours and concentrate in vacuo. Partition between ethyl acetate and aqueous sodium bicarbonate. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo to obtain the product.

EXAMPLE 14

If one were to follow the procedure of Steps A to F, then one would obtain the compound:

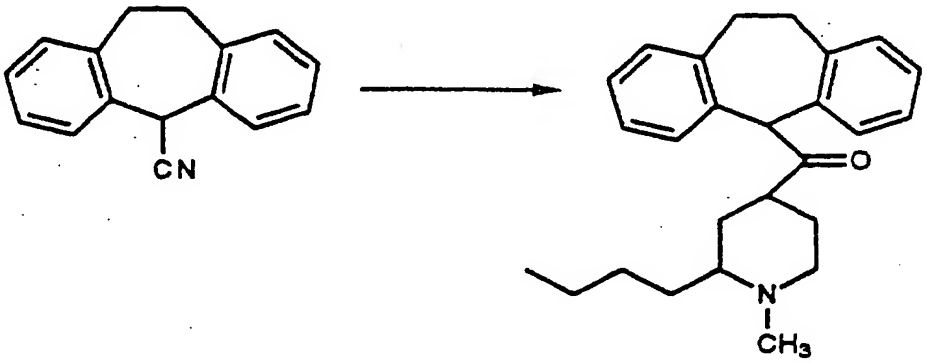


Step A:



5-chlorodibenzosuberane, 48.18 g (0.2 mole), was dissolved in 400 mL of toluene. Silver cyanide, 36.7 g (0.27 mole), was added and the mixture was refluxed for 24 hours. The mixture was cooled, filtered and concentrated in vacuo. The residue was recrystallized from 2-propyl ether and hexane to give 38.8 g of the product. MP = 94.2°-94.9°C.

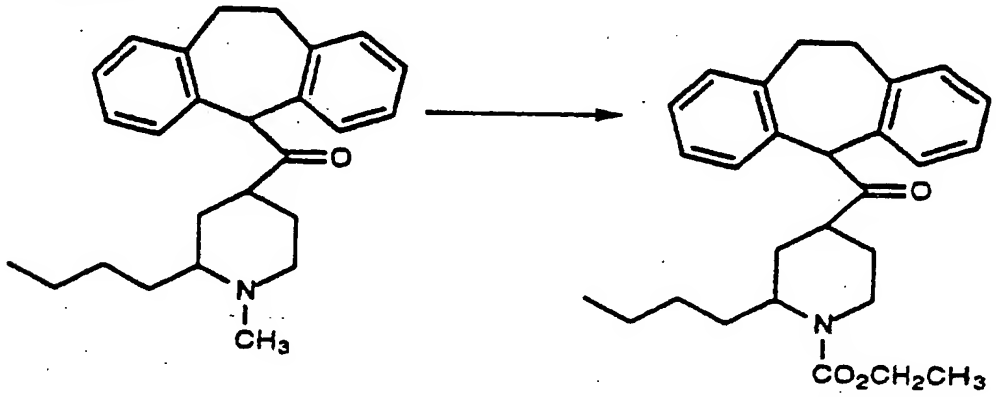
Step B:



Dissolve the product of Example 12, Step E, in THF and add one equivalent of magnesium. Stir until all of the magnesium has reacted. Add this solution dropwise to a solution of one equivalent of the product of

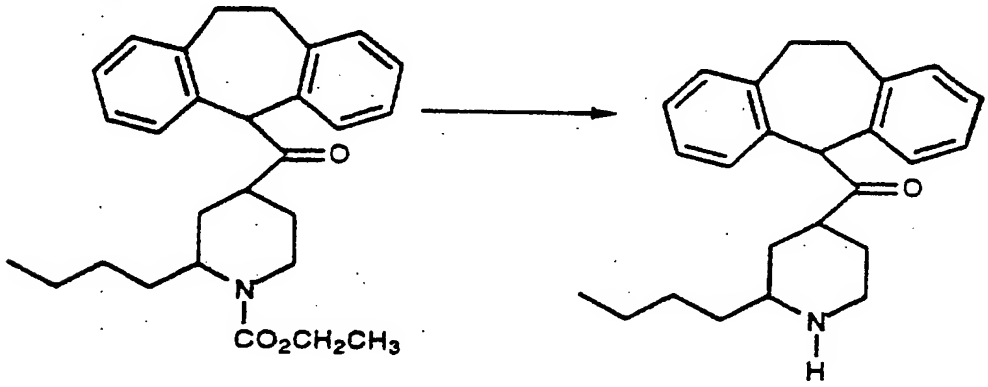
Step A in THF. Stir for 1 hour then quench with aqueous ammonium chloride solution. Extract with ethyl acetate. Dry the organic layer over magnesium sulfate, filter and concentrate under vacuo. Chromatograph on silica gel using methanol-methylene chloride to obtain the product.

Step C:



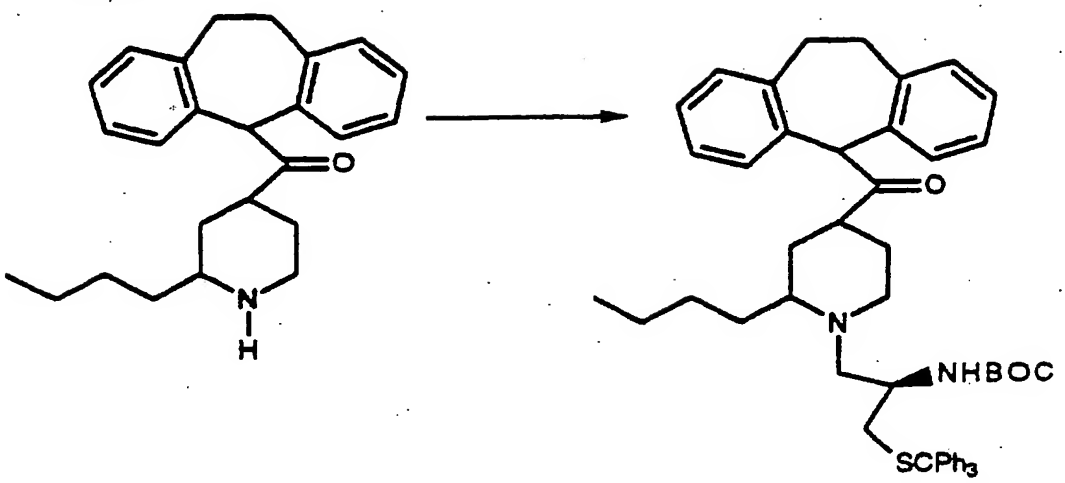
Dissolve the product of Step B in dry toluene containing 2 equivalents of triethylamine. Warm to 80°C and add 9 equivalents of ethyl chloroformate. Stir at 80°C until the reaction is complete, about 2 hours. Filter and concentrate under vacuo. Chromatograph on silica gel using ethyl acetate-hexane to obtain the product.

Step D:



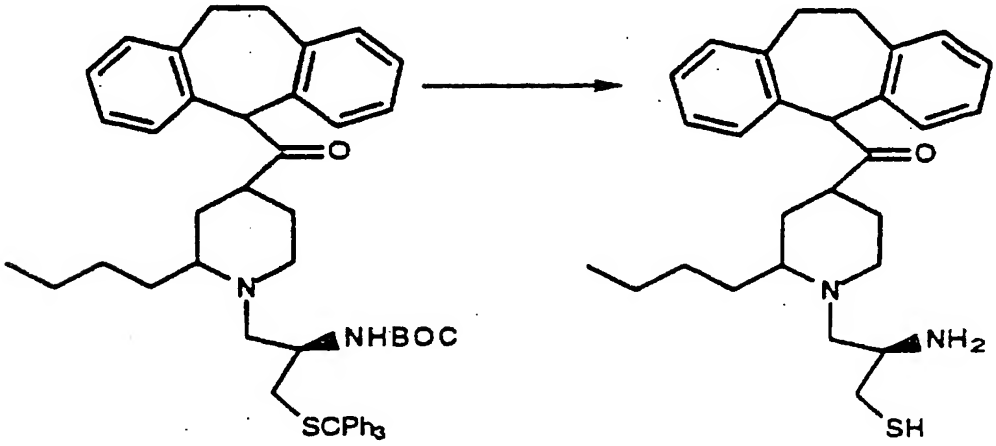
Dissolve the product of Step C in 12 M hydrochloric acid and reflux until complete, about 6 hours. Adjust the pH to 8 with solid sodium hydroxide and filter the precipitated product. Chromatograph on silica gel using methanol-methylene chloride and ammonium hydroxide to give the product.

Step E:



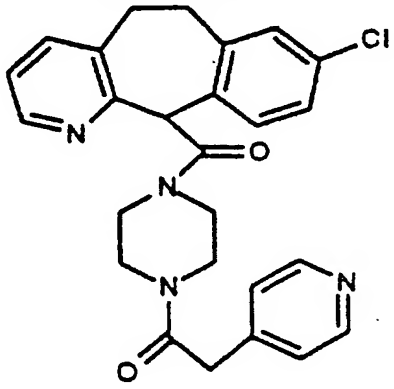
Follow the procedure in Example 1, Step E, to obtain the product.

Step F:



Follow the procedure in Example 1, Step F, to obtain the product.

EXAMPLE 15

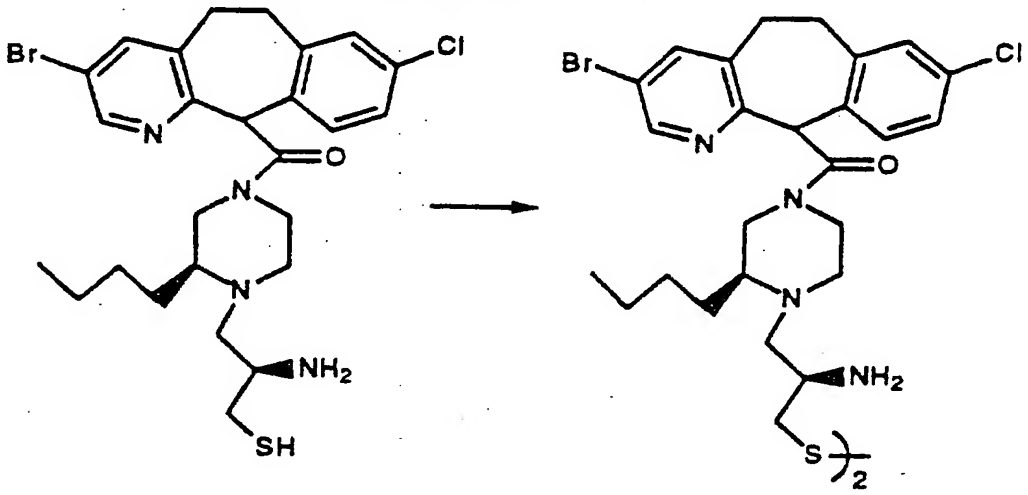


The product of Example 1D was dissolved in DMF and cooled to 0°C under nitrogen. To this solution was added 2 equivalents of 4-pyridyl

acetic acid, 6 equivalents of triethylamine, 2 equivalents of 1-hydroxy-benzotriazole (HOBT), and 2 equivalents of DEC. The reaction mixture was stirred at 0°C overnight. Then the reaction mixture was diluted with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was concentrated under vacuo and the residue was chromatographed on silica gel using methanol-methylene chloride as the solvent. Fractions containing the product were concentrated under vacuo to give the title compound as a white foam. M + 1 = 461.

EXAMPLE 16

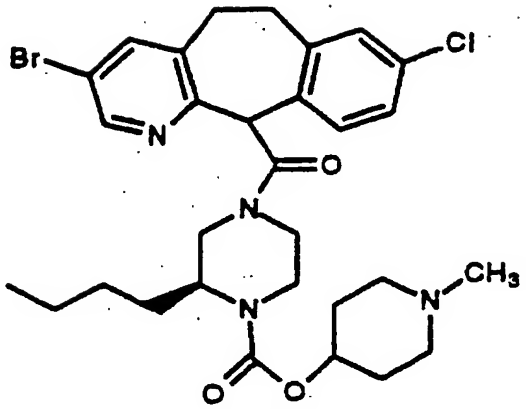
If one were to follow the procedure described below, then one would obtain the indicated compound:



Add a solution of iodine in methanol to the product of Example 3, Step F, in methanol until a slight yellow color persists. Concentrate in vacuo and chromatograph the residue by HPLC using a C_{18} column and a solvent of water-acetonitrile and 0.1% trifluoroacetic acid. Concentrate in vacuo to give the product.

EXAMPLE 17

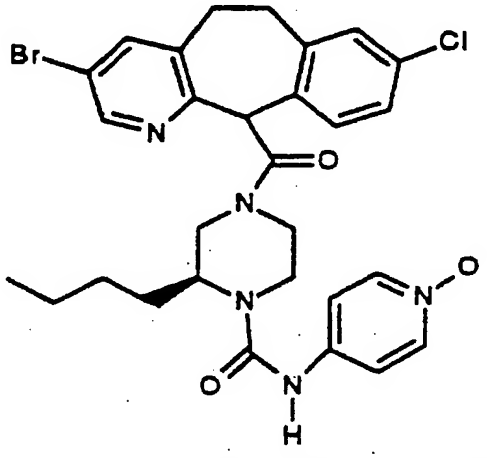
If one were to follow the procedure described, then one would obtain the compound:



React the product of Example 3D with the product of Preparative Example 7 in dichloromethane in the presence of pyridine at 25 °C for 20 to 100 hours to give the title compound.

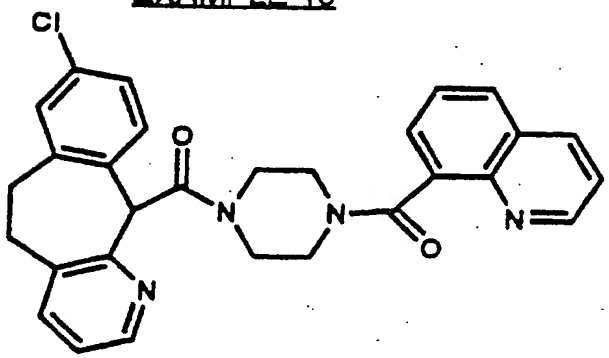
EXAMPLE 18

If one were to follow the procedure described, then one would obtain the compound:

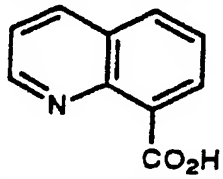


Heat the product (acylazine) from Preparative Example 3 under reflux in anhydrous toluene to convert it into the corresponding isocyanate in situ. Add the product of Example 3D in anhydrous toluene to the mixture and stir this mixture at 25°C for 20 hours to give the title compound.

EXAMPLE 19

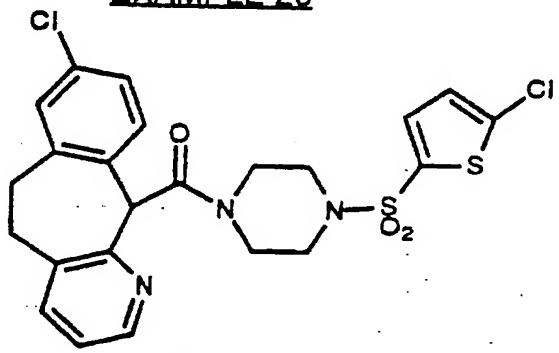


Similar to the procedure in Example 15, the compound of Example 1, Step D, (0.1g) was dissolved in 1.5 mL of DMF and the resulting solution was cooled in an ice bath. The compound:

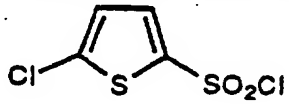


(0.1g, 2eq) was added with stirring until dissolved. Then HOBT (80mg, 2eq), DEC (112mg, 2eq) and N-methylmorpholine (0.3mL, 10eq) were added. The desired product was isolated from the reaction mixture. FAB MS m/e 497 (M+1).

EXAMPLE 20



Similar to the procedure in Example 15, the compound of Example 1, Step D, (0.1g) was dissolved in 1.5mL of pyridine and the resulting solution was cooled in an ice bath. The compound:



(75mg, 1.2eq) was added, and then about 0.1mL of diisopropyl ethyl amine was added. The desired product was isolated from the reaction mixture. MS: m/e 522.

ASSAYS

FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay) was determined by the method disclosed in WO 95/10516. GGPT IC_{50} (geranylgeranyl protein transferase, in vitro enzyme assay), COS Cell (Cell-Based Assay), Cell Mat Assay, and in vivo anti-tumor activity could be determined by the methods disclosed in WO 95/10516.

FPT IC_{50} results were: within the range of 1-10μM for the compound of Example 1; within the range of 10-100μM for the compound of Example 15; >40μM for the compound of Example 19; and within the range of 10-100μM for the compound of Example 20.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams,

lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A - Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B - Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

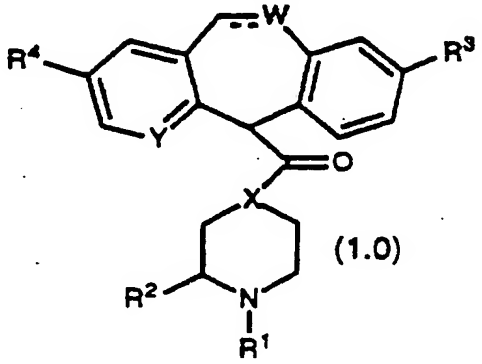
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

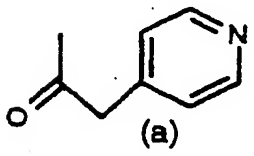
1. A compound of the formula:



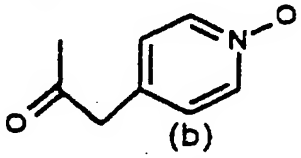
(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

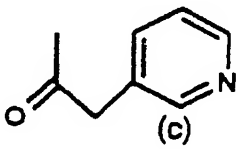
(1) R^1 is a group selected from:



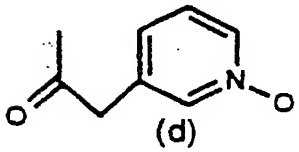
(a)



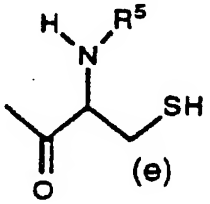
(b)



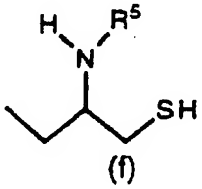
(c)



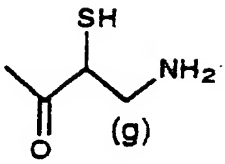
(d)



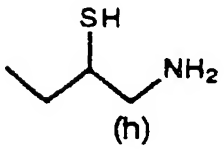
(e)



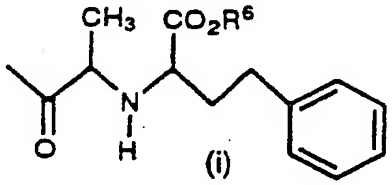
(f)



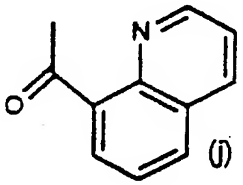
(g)



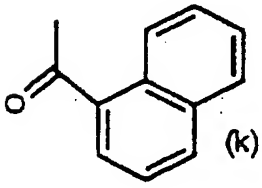
(h)



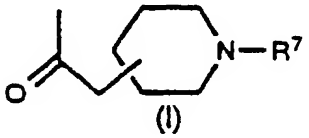
(i)



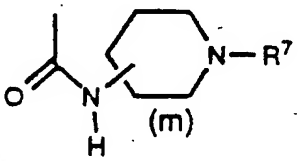
(j)



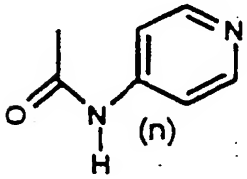
(k)



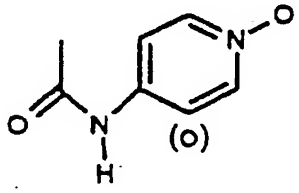
(l)



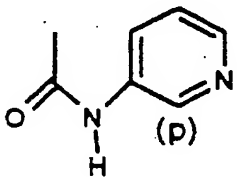
(m)



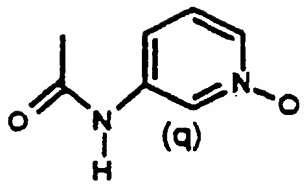
(n)

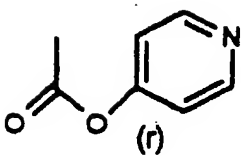


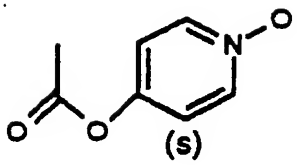
(o)

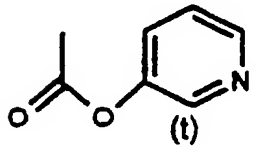


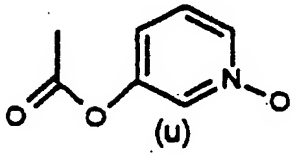
(p)

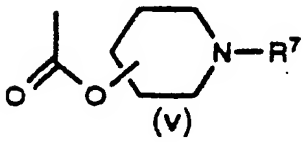

(q)

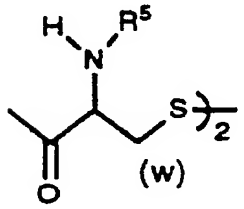

(r)

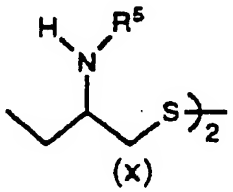

(s)

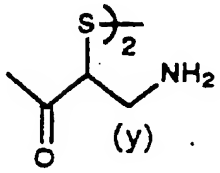

(t)

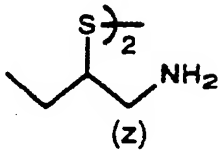

(u)

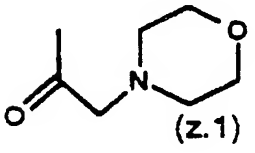

(v)

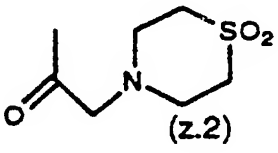

(w)


(x)

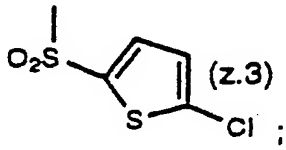

(y)


(z)


(z.1)


(z.2)

or


(z.3)

;

R^2 is selected from:

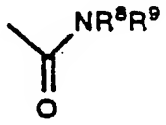
(1) H,

(2) C_1 to C_8 alkyl,

(3) C_2 to C_8 alkenyl,

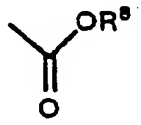
(4) C_2 to C_8 alkynyl,

(5)



, or

(6)



wherein said alkyl, alkenyl, or alkynyl is optionally substituted with one or more groups independently selected from:

(a) aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl; said aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl optionally substituted with one or more groups independently selected from:

(1) C_1 to C_4 alkyl,

(2) $(CH_2)_tOR^8$ wherein t is 1 to 4,
(3) $(CH_2)_tNR^8R^9$ wherein t is 1 to 4, or
(4) halogen,

(b) C_3 to C_6 cycloalkyl,

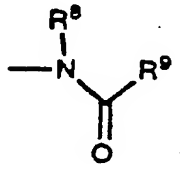
(c) $-OR^8$,

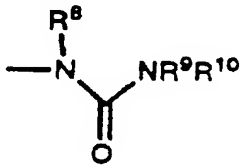
(d) $-SR^8$,

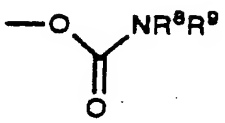
(e) $-S(O)R^8$,

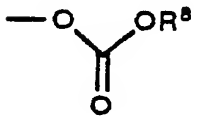
(f) $-SO_2R^8$,

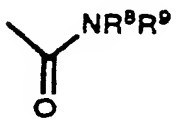
(g) $-NR^8R^9$,

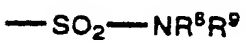
(h) 

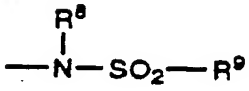
(i) 

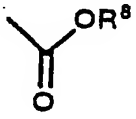
(j) 

(k) 

(l) 

(m) 

(n) 

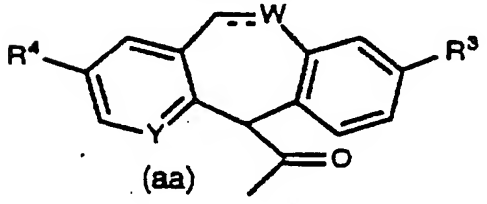
(o) 

;

R^3 is selected from H, halogen or C_1 to C_6 alkyl;

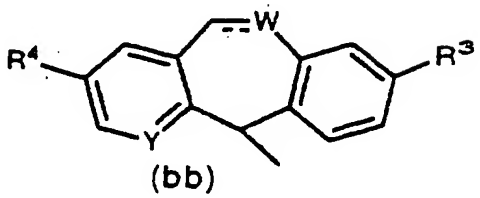
R^4 is seleceted from H, halogen or C_1 to C_6 alkyl;

R^5 is selected from: H,



(aa)

or



(bb)

;

R^6 is selected from H or C_1 to C_6 alkyl;

R^7 is selected from H, C_1 to C_6 alkyl, haloalkyl, or $-C(O)R^{11}$ wherein R^{11} is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy or $-NHR^{12}$ (wherein R^{12} is C_1 to C_6 alkyl or H), or R^7 is an acyl radical of a naturally occurring amino acid;

R^8, R^9 and R^{10} are independently selected from H, C_1 to C_4 alkyl, C_3 to C_6 cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or

aralkyl; said alkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl are optionally substituted with C_1 to C_4 alkoxy, aryl, heteroaryl, heterocycloalkyl, cyclopropyl, halogen, -OH, $-C(O)R^{13}$, $-SO_2R^{13}$, or $-NR^{14}R^{15}$ wherein R^{13} is selected from C_1 to C_4 alkyl or aralkyl, and wherein R^{14} and R^{15} are independently selected from H, C_1 to C_4 alkyl or aralkyl; with the proviso that R^8 is not H in substituents (e), (f) or (k), and with the proviso that R^9 is not H in substituent (h) or (n), and with the proviso that R^8, R^9, or R^{10} is not $-CH_2OH$ or $-CH_2NR^{14}R^{15}$ when R^8, R^9, or R^{10} is directly attached to a heteroatom;

optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which they are bound, form a 5 to 7 membered heterocycloalkyl ring;

optionally, when R^9 and R^{10} are bound to the same nitrogen, R^9 and R^{10}, together with the nitrogen to which they are bound, form a 5 to 7 membered heterocycloalkyl ring;

--- represents an optional bond;

W is selected from CH when the optional bond is present, or O, S or CH_2 when the optional bond is absent;

X is selected from CH or N; and

Y is selected from N or CH.

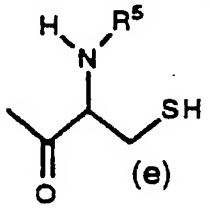
2. The compound of Claim 1 wherein R^3 and R^4 are halogen.

3. The compound of Claim 2 wherein R^3 is Cl and R^4 is Br.

4. The compound of Claim 1 wherein Y is N.

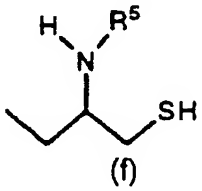
5. The compound of Claim 1 wherein X is N.

6. The compound of Claim 1 wherein R^1 is selected from



(e)

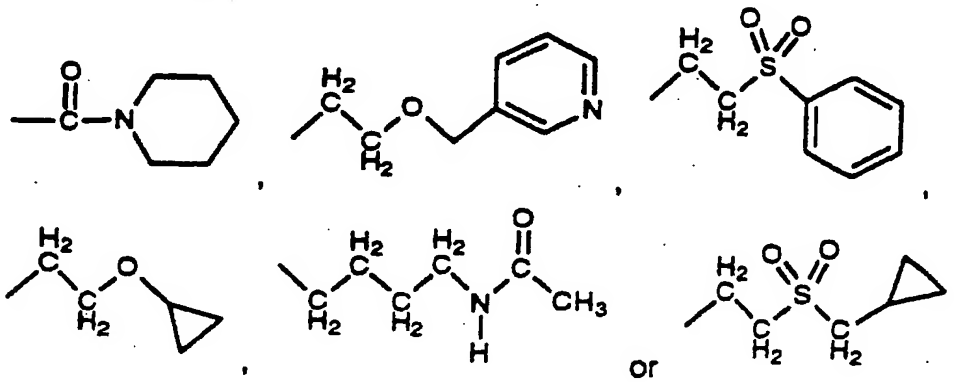
or



(f)

7. The compound of Claim 6 wherein R^5 is H.

8. The compound of claim 1 wherein R^2 is selected from H, $-C_4H_9$, $-CH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2O$-n-C_3H_7, $-CH_2CH_2CH_2OCH_3$,

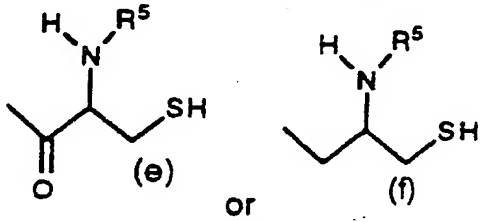


or

9. The compound of Claim 1 wherein W is CH or CH_2, Y is N, and X is N.

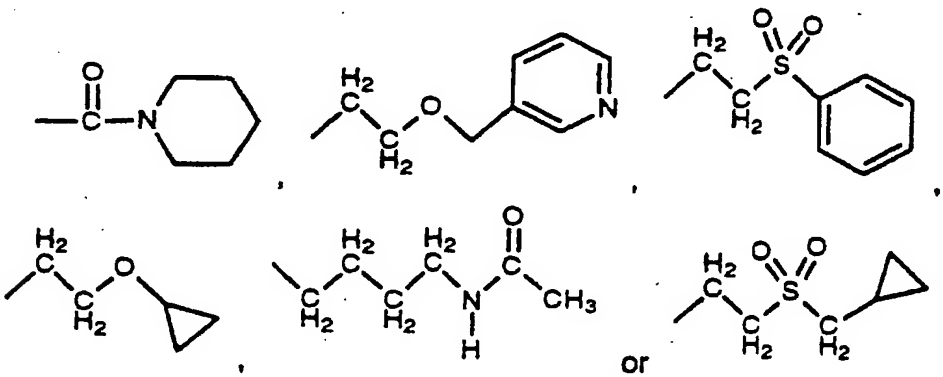
10. The compound of Claim 9 wherein R^3 is Cl and R^4 is Br.

11. The compound of Claim 10 wherein R^1 is selected from



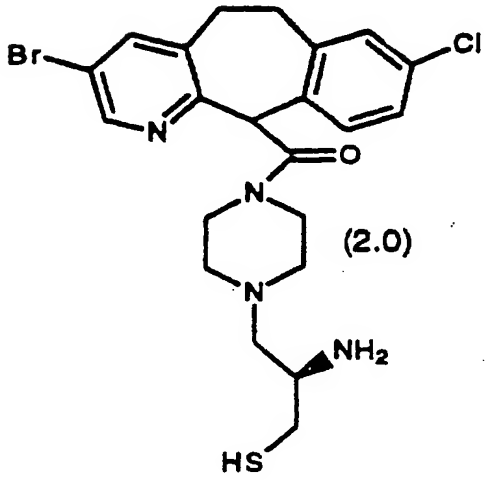
(e) or (f)

wherein R^5 is H, and R^2 is selected from H, $-C_4H_9$, $-CH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2O$-n-C_3H_7, $-CH_2CH_2CH_2OCH_3$,

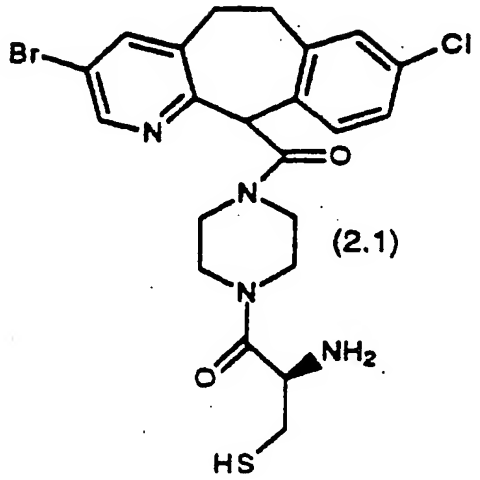


or

12. The compound of Claim 11 having the formula:



or



13. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Claim 1.

14. The method of Claim 13 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

15. The method of Claim 13 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

16. The method of Claim 13 wherein the inhibition occurs by the inhibition of farnesyl protein transferase.

17. The method of Claim 13 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

18. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

19. The use of a compound of Claim 1 for the manufacture of a medicament for inhibiting the abnormal growth of cells.

20. The use of a compound of Claim 1 for inhibiting the abnormal growth of cells.

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